Stereochemical Studies on Cyclopropyl Radicals and Cyclopropanes(Dissertation_全文)

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STEREOCHEMICAL STUDIES
ON
CYCLOPROPYL RADICALS AND CYCLOPROPANES

TAKASHI ISHIHARA

1977

PREFACE

The present work is the collection of the studies which have been performed under the guidance of Professor Teiichi Ando.

The target of the present studies has been put on the investigations of the substituent effect on the configurational stability of cyclopropyl radicals and of the carbon-13 nuclear magnetic resonance spectroscopy for the systems containing the cyclopropane ring, both of which had not been studied systematically at the beginning of these studies.

The thesis consists of three parts. In Part I, the effect of α substituents on the configurational stability of cyclopropyl radicals is described. Part II is concerned with the β-substituent effect on the configurational stability of cyclopropyl radicals. Finally, Part III deals with the carbon-13 NMR spectra of a number of norcarane derivatives.

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PART I

EFFECT OF α SUBSTITUENTS ON THE CONFIGURATIONAL STABILITY OF CYCLOPROPYL RADICALS

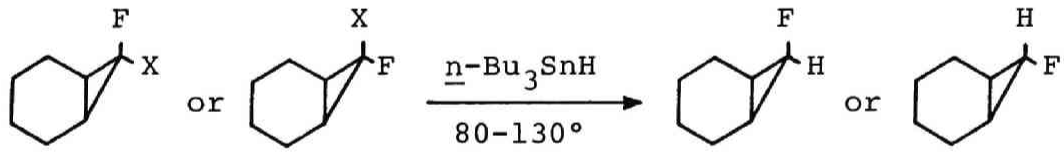
Chapter 1

INTRODUCTION

There has been considerable spectroscopic evidence supporting that ordinary alkyl radicals either have a nonplanar configuration but are subject to rapid inversion of configuration, or have a planar structure. Thus, while studies of the tri- and the difluoromethyl radicals by ESR[1] and of the trifluoromethyl radical by infrared spectroscopy[2] and photoionization[3] indicate that these intermediates have a distinctly nonplanar geometry, the evidence from electronic[4] and electron spin resonance spectra[5] favors a planar structure for the methyl and other unsubstituted alkyl radicals. The fluoro- and the hydroxymethyl radicals are also considered to exist in a nonplanar configuration.[6] In contrast to the spectroscopic evidence, there exists only scattered chemical information about the nature and, in particular, the configurational integrity of α-substituted alkyl radicals.

In this connection, the geometry of cyclopropyl radicals has long been a subject of investigations, and a number of unsuccessful attempts to intercept the nonplanar radical intermediates have been reported.[7] Some notable findings have

recently appeared in the literature;[8-12] for example, Ando and collaborators[8] have reported the extremely high stereospecificity observed in the reduction of gem-halofluorocyclopropanes with tri-n-butyltin hydride, which strongly suggests a pyramidal structure for the intermediate α-fluorocyclopropyl radical and its high configurational stability, or the high energy barrier for inversion.



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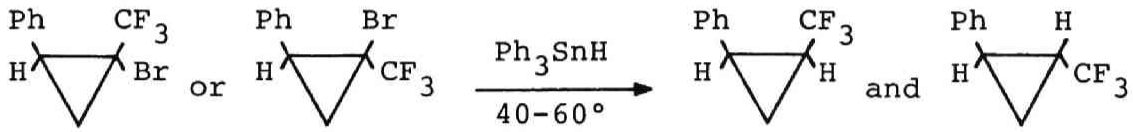
0	100	0	100

On the contrary, a study by Altman, et al.,[9] on the configurational equilibration of the α-(trifluoromethyl)cyclopropyl radical suggests a low configurational stability for this radical intermediate.



100	0	30	70
0	100	31	69

In these studies, however, no systematic investigations on the configurational stability of α-substituted cyclopropyl radicals have been fully undertaken.

This part deals with the effect of α substituents on the configurational stability of cyclopropyl radicals, evaluated by examining the stereochemistry of some reactions which take place *via* α-substituted cyclopropyl radicals, *viz.*, the brominative decarboxylation (Hunsdiecker reaction) of α-substituted cyclopropanecarboxylic acids, the thermal decomposition of their *tert*-butyl peroxy esters, and the reduction of α-substituted cyclopropyl halides with tri-*n*-butyltin hydride.

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Chapter 2

BROMINATIVE DECARBOXYLATION OF 7-SUBSTITUTED NORCARANE-7-CARBOXYLIC ACIDS AND THERMAL DECOMPOSITION OF THEIR PEROXY ESTERS[1]

The stereochemistry of the brominative decarboxylation of endo-7-fluoro- (Ia), exo-7-fluoro- (Ib), endo-7-chloro- (IIa), and exo-7-chloronorcarane-7-carboxylic acid (IIb), as well as the thermal decomposition of their tert-butyl peroxy esters in toluene, cumene, or bromotrichloromethane, has been examined. The degree of stereospecificity observed in these reactions has revealed that (i) the 7-fluoro-7-norcaryl radical is configurationally very stable and its bromine abstraction under the brominative decarboxylation conditions (0 or 77°) or from bromotrichloromethane (110°) occurs much more rapidly than its inversion of configuration, (ii) its hydrogen abstraction from toluene or cumene occurs less rapidly and can compete with its inversion, and (iii) the inversion of the 7-chloro-7-norcaryl radical occurs more rapidly than that of the corresponding fluoro radical, and consequently the stereospecificity of the reaction involving the chloro radical decreases. Similar reactions of 7-unsub-

stituted norcarane-7-carboxylic acids (IIIa and IIIb) and their peroxy esters have shown that the 7-norcaryl radical is configurationally unstable and behaves like a planar radical in these reactions.

Based on many spectrochemical data, ordinary alkyl radicals have been recognized either to have a pyramidal structure but be subject to rapid inversion of configuration, or to have a planar structure. For example, the trifluoromethyl radical has been proved to be pyramidal by ir[2] and ESR[3] spectroscopy and by photoionization studies.[4] The fluoro- and the hydroxymethyl radicals are also considered to be pyramidal,[5] whereas electronic[6] and ESR[7] spectra have provided evidence supporting a planar structure for the methyl and other unsubstituted alkyl radicals.

Recent chemical studies on the nature and, in particular, the configurational stability of vinyl[8] and cyclopropyl[9] radicals have favored a bent and a nonplanar configuration, respectively, at the tervalent carbon. Thus, it was reported that the reduction of some gem-halofluorocyclopropanes with tri-n-butyltin hydride proceeded with complete retention of configuration.[9a,b] The results were rationalized by postulating a pyramidal structure for the intermediate α-fluorocyclopropyl radical and the slow rate of its inversion relative to its hydrogen abstraction, which came from the high configurational stability, or the high energy barrier

for inversion, of the α-fluorocyclopropyl radical.

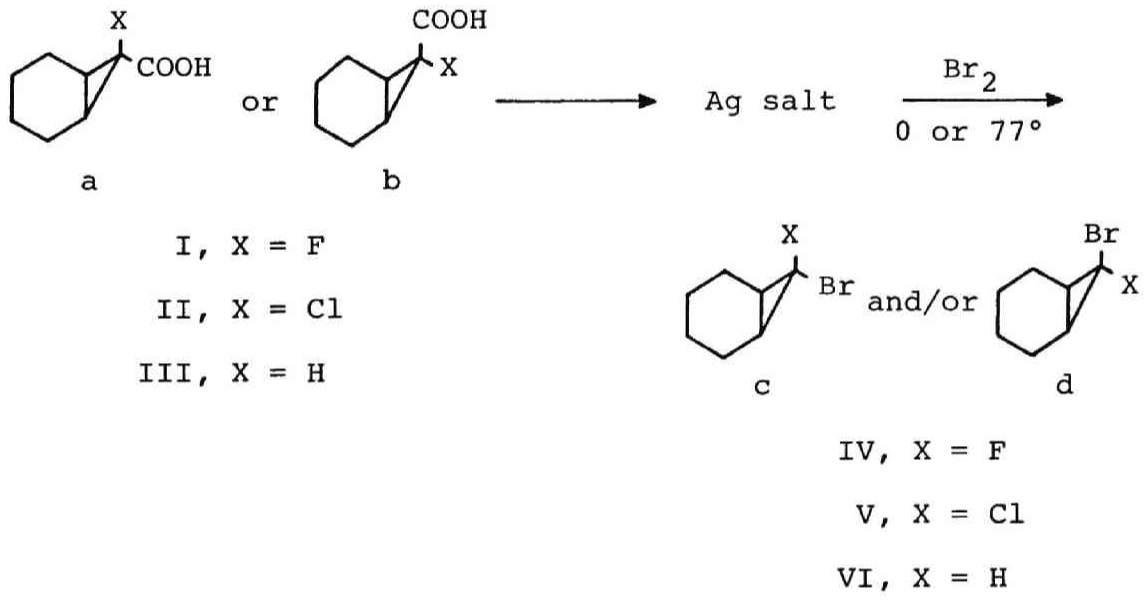
The validity of this assumption has now been examined by studying the stereochemistry of some reactions which are believed to involve α-fluoro(or -chloro)cyclopropyl radicals, viz., the brominative decarboxylation (Hunsdiecker reaction) of 7-halonorcarane-7-carboxylic acids and the thermal decomposition of their peroxy esters.

RESULTS

BROMINATIVE DECARBOXYLATION OF 7-HALONORCARANE-7-CARBOXYLIC ACIDS (I, II, AND III). Two isomers of 7-fluoronorcarane-7-carboxylic acid (Ia and Ib) (Scheme I) were obtained by carbonation of 7-fluoro-7-norcaryllithium followed by fractional recrystallization. The configurational assignment to the isomers was made from their ^{19}F NMR spectra based upon the generalization that in fluorocyclopropanes the ring fluorine is more strongly coupled with cis than with trans hydrogen,[10] and that in alkyl- and aryl-substituted cyclopropanes the ring fluorine is shielded by cis and deshielded by trans substituents.[11] Isomers of 7-chloronorcarane-7-carboxylic acid (IIa and IIb) were prepared according to the method of Köbrich and Goyert.[12] The 7-unsubstituted acids, IIIa and IIIb, were prepared as follows: norcarane-exo-7-carboxylic acid (IIIa) was obtained by the reaction of ethyl diazoacetate with cyclohexene followed by alkaline hydrolysis and fractional recrystallization. Endo acid IIIb was obtain-

ed by the reduction of methyl 7-bromonorcarane-7-carboxylate with tri-n-butyltin hydride followed by hydrolysis. Their spectral data were in good agreement with the reported ones.[12,13,14]

SCHEME I



The silver salts of the acids were separately prepared in the conventional manner and were allowed to react with bromine in carbon tetrachloride under the conditions indicated in Table I. The brominated cyclopropanes were identified by comparison of their retention times and spectral properties with those of an authentic sample of 7-bromo-7-fluoronorcarane, 7-bromo-7-chloronorcarane, or 7-bromonorcarane. The yields of these bromides were determined from

TABLE I

Brominative Decarboxylation

of 7-Halonorcarane-7-carboxylic Acids (I, II, and III)[a]

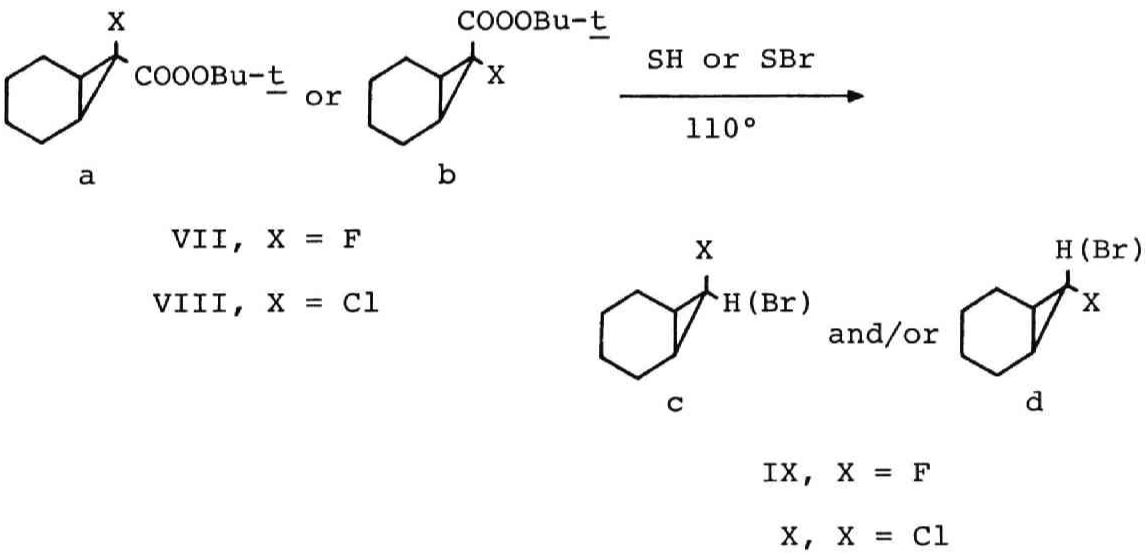
Compd	Time hr	Temp °C	Yield %	Isomer ratio retn : invn
Ia	2	0	71	100 : 0
	2	77	75	100 : 0
Ib	2	0	75	100 : 0
	2	77	71	100 : 0
IIa	2	0	68	88 : 12
	2	77	73	72 : 28
IIb	2	0	71	82 : 18
	2	77	74	43 : 57
IIIa	2	0	70	81 : 19
	2	77	73	84 : 16
IIIb	2	0	72	16 : 84
	2	77	76	15 : 85

[a] In all runs, no ring-opening products were detected by GLC.

their peak areas in GLC, calibrated against authentic sample solutions of known concentrations.

THERMAL DECOMPOSITION OF tert-BUTYL PEROXY ESTERS (VII AND VIII). tert-Butyl 7-fluoro- and 7-chloronorcarane-7-peroxycarboxylates were prepared in good yields by treatment of the corresponding acid chloride with tert-butyl hydroperoxide in n-pentane at -20°. The peroxy esters were purified

SCHEME II



by chromatography on Kiesel gel prior to use. All four peroxy esters gave satisfactory spectral analyses. Two of the four peroxy esters were solids at room temperature (VIIa, mp 40.0-41.0°; VIIIa, mp 46.5-47.5°), which minimized con-

TABLE II

Thermal Decomposition

of tert-Butyl Peroxy Esters (VII and VIII)[a]

Compd	Solvent	Yield, %[b] RCOOH	RH or RBr	Isomer ratio retn : invn
VIIa	Toluene	13	61	94 : 6
	Cumene	15	65	96 : 4
	$CBrCl_3$		53	100 : 0
VIIb	Toluene	16	65	90 : 10
	Cumene	16	58	93 : 7
	$CBrCl_3$		49	100 : 0
VIIIa	Toluene	17	64	78 : 22
	Cumene	18	56	80 : 20
	$CBrCl_3$		38	82 : 18
VIIIb	Toluene	18	68	23 : 77
	Cumene	19	55	21 : 79
	$CBrCl_3$		47	18 : 82

[a] See footnote a in Table I. [b] R stands for 7-fluoro- or 7-chloro-7-norcaryl group.

tamination problems, and the others (VIIb and VIIIb) were liquids at room temperature. The structural assignment of all peroxy esters was made on the basis of the stereochemistry of the starting acids.

Degassed solutions of the peroxy esters in toluene, cumene, or bromotrichloromethane as scavenging solvent were heated in sealed Pyrex ampoules at 110° for 24 hr (Scheme II). Infrared analysis revealed no remaining peroxy esters at the end of the reaction. The yields of the products are given in Table II together with the reaction conditions. The products formed by hydrogen (or bromine) abstraction, RH or RBr, were identified by comparison with authentic samples and their yields were measured by the internal standard method (GLC). Where only relative yields (isomer distributions) were desired, no internal standard was added. The yields of acids, RCOOH, were determined by calibration of the carboxyl absorption intensity against those of solutions of known concentrations. The isolated acids were found to have retained the geometry of the starting peroxy esters in all cases.

DISCUSSION

As shown in Table I, the brominative decarboxylation of 7-fluoronorcarane-7-carboxylic acid (I) occurred with complete retention of configuration, whereas that of the chloro acid II occurred with only partial stereospecificity to give

a mixture of two geometrical isomers. The high stereospecificity observed with the fluoro acid means that the inversion of configuration of the 7-fluoro-7-norcaryl radical occurs much more slowly than its bromine abstraction, and can be ascribed to the extremely high configurational stability of the α-fluorocyclopropyl radical intermediate as previously cited.[9b] On the other hand, the stereochemical behavior of the chloro acid suggests that the configurational stability of the 7-chloro-7-norcaryl radical is not so high as that of the corresponding fluoro radical, and that the inversion of the chloro radical occurs at a rate comparable to its bromine abstraction. Table I also shows that, as is the case in the reduction of cyclopropyl bromides with tri-n-butyltin hydride,[9b] the ratio of retention to inversion decreases as the temperature increases.

In the reaction of the corresponding 7-unsubstituted acid (III) under the same reaction conditions, the isomer distributions in the products were nearly identical in all runs, irrespective of the geometry of the starting acid. This indicates that the unsubstituted 7-norcaryl radical is either pyramidal but inverts its configuration so rapidly that it behaves like a planar radical, or in fact it is planar.

From the above-described results, it follows that both the α-fluoro and the α-chloro substituents can stabilize the pyramidal configuration of the cyclopropyl radical, but the effect of fluorine is much stronger than that of chlorine.

Further evidence supporting this view is provided by

the thermal decomposition of the tert-butyl peroxy esters of 7-fluoro- and 7-chloronorcarane-7-carboxylic acid (VII and VIII).

The significant yields of the acids suggest that a one-bond homolysis[15] operates with these peroxy esters. However, decarboxylation also occurs as indicated by the moderate to high yields of RH (Table II). As is clear from the data in Table II, the hydrogen abstraction of the 7-fluoro-7-norcaryl radical from toluene or cumene is not so rapid as the bromine abstraction from bromotrichloromethane and can compete with the inversion of configuration. It should be noted that the degree of stereospecificity is closely related to the bond-dissociation energy of the C-H or the C-Br bond in scavenger molecules.

In contrast with the fluoro peroxy esters, the isomer compositions of the products from the chloro peroxy esters are essentially the same, regardless of their stereochemistry. It means that, at least at this reaction temperature, the inversion of configuration of the chloro radical takes place much more rapidly than the hydrogen or bromine abstraction from the solvents, though more efficient scavenging systems might lead to partial or complete specificity. The preferential formation of endo-chloronorcarane and endo-chloro-exo-bromonorcarane (Xc) is most easily explained by stereoselectivity in the hydrogen or bromine abstraction step, i.e., the approach of the scavenging agent toward the 7 position from the exo side being sterically less hindered than that from the endo side.

A similar trend has been noted in studies on the 9-decalyl systems[16] where a change of solvent from cyclohexane to cumene leads to an increase in cis-decalin in the product mixture.

From the stereochemical results described herein, it may be concluded that in comparison with the α-fluorocyclopropyl radical, the configurational stability of the α-chloro radical is lower, but not so low as that of the α-unsubstituted one.

Generally, the configurational stability of free radicals can be regarded as being dependent upon the s character of the odd-electron orbital.[17] Thus, vinyl radicals are configurationally more stable than cyclopropyl radicals, since the odd-electron orbital of the former is sp^2 hybridized and that of the latter is $sp^{2.4}$ or $sp^{2.5}$ hybridized.[18] If the α hydrogen is replaced by an electronegative atom or group such as fluorine or chlorine, the s character of the carbon orbital forming the C-F or the C-Cl bond decreases relative to that of the C-H bond, and as a result the s character of the odd-electron orbital increases. It may be expected, therefore, that the more electronegative the α substituent is, the less rapidly the inversion of configuration will occur.

The results reported herein are in accordance with this expectation. An analogous tendency has been observed with α-substituted vinyl radicals,[8] and the calculation of the energy barrier for inversion of some cyclopropyl and vinyl radicals by CNDO/2[9c] or MINDO/3[19] also suggests the significance of the electronegativity effect of α substituents. The work

of Altman, et al.,[9d] on the α-(trifluoromethyl)cyclopropyl radical reveals, however, that the electronegativity can not be the only factor that determines the configurational stability of cyclopropyl radicals. No doubt more work must be done, both theoretically and experimentally, in order to solve the problem.

EXPERIMENTAL SECTION

All boiling and melting points are uncorrected. Infrared spectra were taken on a Shimadzu IR-27 infrared spectrometer using a polystyrene film for calibration. Proton NMR spectra were measured for solutions in carbon tetrachloride with tetramethylsilane (Me_4Si) as an internal standard with a Varian Associates T-60 or A-60 or a Jeolco H-60 spectrometer (60 MHz). Fluorine NMR spectra were recorded on a Hitachi H-60 spectrometer (56.4 MHz) in carbon tetrachloride with trifluoroacetic acid (TFA) as an external reference. The proton and fluorine chemical shifts are expressed in parts per million downfield from Me_4Si and in parts per million upfield from TFA, respectively. Gas chromatographic (GLC) analyses were performed with a Shimadzu GC-2C or a Hitachi K23 gas chromatograph by use of a 3 m x 3 mm column with 7% Apiezon L or 7% Silicon DC 550 on 80-100 Celite 545, or a 45 m x 0.25 mm Golay column with Apiezon L or butanediol succinate (BDS). Isomer distributions were calculated from peak areas in gas chromatograms. The values of the isomer ratios listed in Tables I and II are ac-

curate within ±2%.

MATERIALS. All chemicals were reagent grade and used without further purification. Solvents were distilled (or vacuum distilled) through a 25-cm Vigreux column and, if necessary, were purified in the usual manner prior to use. Authentic samples were prepared as follows: 7-bromo-7-fluoronorcarane and 7-bromo-7-chloronorcarane were obtained by the reaction of cyclohexene with bromofluorocarbene[9a,20] and bromochlorocarbene,[21] respectively, generated by basic decomposition of the corresponding trihalomethane.

7-FLUORONORCARANE-7-CARBOXYLIC ACID (I). To a solution of 29g (0.15 mol) of 7-bromo-7-fluoronorcarane (mixture of isomers) in 200 ml of tetrahydrofuran-ether (1:1), cooled to -140° by immersing in a bath of liquid nitrogen and methylcyclohexane-n-hexane (4:1), was added, under nitrogen atmosphere, 200 ml of a 0.7N solution of n-butyllithium in n-hexane at such a rate that the temperature should not rise above -130°. After the addition was over, the reaction mixture was stirred for 20 hr at -150 to -140°, and then an excess of solid carbon dioxide was carefully added. The mixture was warmed up to room temperature, poured onto ice water, and was worked up as usual. From the acid fraction, 2.1-2.5g of 7-fluoronorcarane-7-carboxylic acid was obtained together with 3-4g of n-valeric acid. The neutral fraction gave 6-7g of unchanged 7-bromo-7-fluoronorcarane (exo F : endo F = 9 : 1), ca. 2g of 7-(2-tetrahydrofuryl)norcarane, and a small amount of some unidentified products. The crude acid thus prepared was fractionally recrystallized from petroleum ether to yield

1.4-1.7g of the exo-fluoro isomer (Ib), mp 99.0-99.5°, and 0.2-0.4g of the endo-fluoro isomer (Ia), mp 112.5-113.0°.

Ia: ir (KBr) 1720 (vs), 1440 (s), 1308 (m), 1265 (s), 1250 (s), 1176 (s), 1122 (s), 1035 (m), 980 (m), 790 (m), 755 (m), 680 cm^{-1} (m); ^{1}H NMR δ 1.1-2.3 (complex m, 10H) and 11.94 (s, 1H); ^{19}F NMR δ_F 146.0 (J_{HF} = 5.9 Hz).

Anal. Calcd for $C_8H_{11}O_2F$: C, 60.75; H, 7.01; F, 12.01. Found: C, 61.02; H, 7.22; F, 12.02.

Ib: ir (KBr) 1703 (vs), 1690 (vs), 1440 (vs), 1300 (s), 1220 (vs), 1195 (s), 1122 (s), 1095 (s), 1040 (m), 910 (s), 850 (m), 780 cm^{-1} (s); ^{1}H NMR δ 0.8-2.2 (complex m, 10H) and 11.85 (s, 1H); ^{19}F NMR δ_F 98.2 (J_{HF} = 22.3 Hz).

Anal. Calcd for $C_8H_{11}O_2F$: C, 60.75; H, 7.01; F, 12.01. Found: C, 60.83; H, 6.93; F, 12.14.

7-CHLORONORCARANE-7-CARBOXYLIC ACID (II) was prepared according to the method by Köbrich and Goyert.[12]

IIa: mp 92.0-92.5°; ir (KBr) 1680 (vs), 1440 (m), 1290 (s), 1170 (m), 1105 (m), 1000 (m), 900 (m), 780 (m), 728 cm^{-1} (m); ^{1}H NMR δ 1.0-2.2 (complex m, 10H) and 12.63 (s, 1H).

IIb: mp 108.0-109.0°; ir (KBr) 1683 (vs), 1440 (s), 1310 (s), 1221 (s), 1170 (m), 1060 (m), 975 (m), 840 (m), 780 (m), 750 cm^{-1} (m); ^{1}H NMR δ 1.1-2.0 (complex m, 10H) and 12.42 (s, 1H).

NORCARANE-7-CARBOXYLIC ACID (III). To 74g (0.9 mol) of cyclohexene in the presence of ca. 0.5g of anhydrous cupric sulfate was carefully added, at room temperature, a solution of 34g (0.3 mol) of ethyl diazoacetate which had been diluted with an equal volume of ether. After the addition, the mix-

ture was stirred until the evolution of nitrogen ceased, and then was worked up as usual. Vacuum distillation of the organic layer afforded, together with ethyl maleate, an isomeric mixture of ethyl norcarane-7-carboxylate (exo ester : endo ester = 9 : 1), bp 72-77° (3 mm), which was hydrolyzed with potassium hydroxide in 50% aqueous ethanol. After a usual work-up, the acid fraction was distilled in vacuo to give crude acid, bp 111-113° (3 mm). Recrystallization from petroleum ether gave 5.5g of pure norcarane-exo-7-carboxylic acid (IIIa) in an overall yield of 13%: mp 95.0-96.0°; ir (KBr) 1673 (vs), 1450 (s), 1310 (s), 1233 (s), 1000 (m), 785 (m), 698 cm^{-1} (m); ^{1}H NMR δ 0.9-2.0 (complex m, 11H) and 12.38 (s, 1H). The reduction of 23g (0.12 mol) of methyl 7-bromonorcarane-7-carboxylate with 35g (0.12 mol) of tri-n-butyltin hydride at 0° gave 13.9g of an isomeric mixture (endo ester : exo ester = 13 : 1) in 90% yield, bp 93-94° (19 mm). By a similar treatment as above, 7.0g of norcarane-endo-7-carboxylic acid (IIIb) was obtained as a crystalline solid: 51% yield; mp 77.0-78.0°; ir (KBr) 1690 (vs), 1450 (s), 1345 (m), 1205 (vs), 1170 (s), 1140 (m), 980 (m), 870 (m), 780 cm^{-1} (m); ^{1}H NMR δ 0.9-2.1 (complex m, 11H) and 12.18 (s, 1H).

BROMINATIVE DECARBOXYLATION OF ACIDS (I, II, AND III). In a three-necked flask equipped with a thermometer, a dropping funnel, a stirrer bar, and a condenser with a drying tube at the top was placed 5-10 mmol of the silver salt of I, II, or III and 20 ml of carbon tetrachloride. This suspension was maintained at a constant temperature (0 or 77°) and a solution of 1.2 equiv of bromine in 10 ml of carbon tetrachloride

was rapidly added with stirring. After being kept at the same temperature for 2 hr, the reaction mixture was brought to room temperature. The silver-containing precipitates were removed by filtration and washed with a small amount of carbon tetrachloride. The filtrates were concentrated by vacuum evaporation below 30°. The residue was carefully distilled under reduced pressure. The isomer composition of the product was determined by GLC prior to distillation and is shown in Table I.[22]

PREPARATION OF tert-BUTYL PEROXY ESTERS (VII AND VIII). A solution of pyridine (15 mmol) and the acid chloride (10 mmol), prepared by conventional methods from thionyl chloride, in 10 ml of n-pentane was cooled in an ice-salt bath, and to it was added a solution of 98% tert-butyl hydroperoxide (50 mmol) in 10 ml of n-pentane. The mixture was stirred for 3 hr at -15 to -20° and for 1 hr at room temperature. The organic layer was washed successively with cold 10% sulfuric acid, cold 10% aqueous sodium carbonate, and water. It was dried over anhydrous sodium sulfate and concentrated in vacuo to a slightly green oil. The product was purified by chromatography on Kiesel gel G (Merck) to give a clear oil or a solid in 55-61% yields.

VIIa: mp 40.0-41.0°; ir (CCl_4 solution) 1760 (vs), 1375 (s), 1350 (s), 1050 (s), 1032 cm^{-1} (s); ^1H NMR δ 1.39 (s, 9H) and 1.2-1.9 (complex m, 10H).

VIIb: colorless liquid; ir (film) 1770 (vs), 1365 (s), 1328 (s), 1200 (s), 1150 (vs), 1080 (vs), 1030 cm^{-1} (s); ^1H NMR δ 1.39 (s, 9H) and 1.2-2.0 (complex m, 10H).

VIIIa: mp 46.5-47.5°; ir (CCl_4 solution) 1755 (vs), 1370 (s), 1215 (vs), 1190 (s), 1155 (vs), 1052 (m), 1030 cm^{-1} (m); ^1H NMR δ 1.36 (s, 9H) and 1.3-2.0 (complex m, 10H).

VIIIb: colorless liquid; ir (film) 1775 (vs), 1365 (s), 1295 (s), 1176 (s), 1145 (vs), 1080 (s), 1025 cm^{-1} (m); ^1H NMR δ 1.36 (s, 9H) and 1.3-2.0 (complex m, 10H).

THERMAL DECOMPOSITION OF tert-BUTYL PEROXY ESTERS (VII AND VIII). A solution of 0.5-1.0 mmol of the peroxy ester in a tenfold molar quantity of toluene, cumene, or bromotrichloromethane was placed in a pressure-resistant Pyrex ampoule. It was degassed with pure nitrogen and was heated at 110° for 24 hr. After the reaction was over, the reaction mixture was cooled to 0°, and the ampoule was carefully opened. The isomer distribution in the product was determined by GLC prior to any treatments and is shown in Table II.[22]

The free acids were isolated by conventional extraction methods. The comparison of the spectral properties and melting points of the isolated acids with those of authentic samples showed the geometry of the starting peroxy esters being retained.

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(22) It was confirmed, by separate experiments, that the isomer ratios given in Tables I and II showed no appreciable change, and no ring-opening products were detected by GLC, after the reaction mixture was kept under the reaction conditions for an additional 4 and 10 hr, respectively.

Chapter 3

REDUCTION OF 7-SUBSTITUTED 7-HALONORCARANES WITH TRI-n-BUTYLTIN HYDRIDE

Isomers of 7-methyl-7-chloronorcarane were reduced with tri-n-butyltin hydride to give a mixture of endo- and exo-7-methylnorcarane, whose endo : exo ratio was 70 : 30 irrespective of the geometry of the starting chloride. Reduction of isomers of 7-phenyl-7-chloronorcarane proceeded similarly, to give 7-phenylnorcarane with the endo : exo ratio of 90 : 10. The lack of stereospecificity in these reactions suggests that the 7-methyl- and the 7-phenyl-7-norcaryl radicals are configurationally unstable and behave as if they were planar in these reactions.

Previous work on the stereochemical behavior of α-substituted cyclopropyl radicals has revealed that the electronic nature of the substituent at the position α to the radical center has a profound effect on the configurational stability, or the energy barrier for inversion, of cyclopropyl rad-

icals.[1-8] In the literature, however, there have been no systematic investigations on the effect of α-alkyl and α-aryl substituents on the configurational stability of cyclopropyl radicals. Such information should be of importance in clarifying the substituent effect of this type.

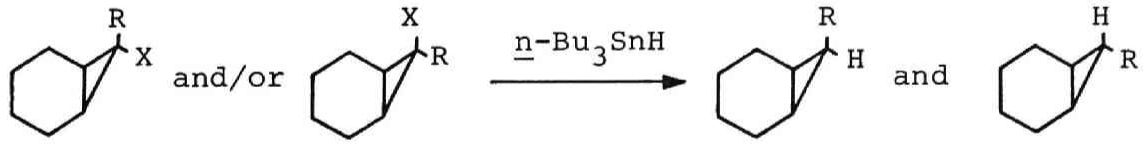
This chapter deals with the results of the reduction of 7-methyl- and 7-phenyl-7-chloronorcarane with tri-n-butyltin hydride as well as that of 7-bromo-7-chloronorcarane.

RESULTS AND DISCUSSION

The norcarane derivatives employed for the present study, i. e., 7-chloro-7-methylnorcarane (I), 7-chloro-7-phenylnorcarane (II), and 7-bromo-7-chloronorcarane (III), were prepared from the treatment of 7,7-dichloronorcarane with n-butyllithium followed by methylation or bromination, or from the addition of the corresponding halocarbene (or carbenoid) to cyclohexene (See Experimental Section). The assignment of configuration to the compounds I and III was based upon the carbonation of 7-chloro-7-norcaryllithium,[9] which at -80° gave predominantly the endo acid isomer of 7-chloronorcarane-7-carboxylic acid and at -120° produced a mixture of the two possible geometrical isomers. The stereochemistry of 7-chloro-7-phenylnorcarane (II) was determined from the difference in rate of the thermal decomposition of the isomers, on the basis of that found in the ring expansion of 7,7-dihalonorcaranes in hot quinoline.[10] This configurational as-

signment was further confirmed by their carbon-13 NMR spectra, which will be discussed later (See Part III in this thesis).

SCHEME



a b c d

I, R = Me; X = Cl

II, R = Ph; X = Cl

III, R = Cl; X = Br

IV, R = Me

V, R = Ph

VI, R = Cl

The reduction of these compounds was performed by treating them with 1.2 equiv of neat tri-n-butyltin hydride under the variety of conditions shown in Tables I and II. The yields of the reduction products were determined by the internal standard method (GLC). Where only relative yields (isomer distributions) were desired, no internal standard was added. The isomer distributions in the products, which were determined before distillation, are also listed in Tables I and II.

As is evident from Table I, the isomer ratios of the products were nearly identical in all experimental runs. This implies that the 7-methyl- or the 7-phenyl-7-norcaryl

TABLE I

Reduction of Halides (I and II) with Tri-n-butyltin Hydride

Compd	Temp °C	Catalyst	Time hr	Yield %	Isomer ratio c : d
Ia	80	AIBN	6	77	73 : 27
	140	DTBP	4	86	71 : 29
Ib	80	AIBN	6		71 : 29
	140	DTBP	4		70 : 30
IIa + IIb*	80	AIBN	8	64	91 : 9
	140	DTBP	4	77	89 : 11
IIb	80	AIBN	8	72	90 : 10
	140	DTBP	4	73	88 : 12

* Isomer ratio, IIa : IIb = 40 : 60.

radical, which would be intermediately formed in the process of the reduction, is either pyramidal but inverts its configuration so rapidly that it behaves as if it were planar, or is in fact planar. Very probably the energy barrier for inversion of configuration of the 7-phenyl-7-norcaryl radical is lowered by virtue of the p-π conjugation between the π electrons in the phenyl substituent and the p electron at the radical center, as suggested earlier to explain the similar results of the reduction of 7-methoxycarbonyl- and 7-

cyano-substituted 7-halonorcaranes.[3]

The predominant formation of the endo-substituted isomers, IVc and Vc, in these reductions should be due to the greater steric repulsion in the hydrogen transfer from the tin hydride to the endo side of the radical than to the exo side. The increase in the relative amount of the exo-substituted isomer with an increase in the reaction temperature may be explained on the same ground.

In contrast, the results in Table II show that the reduction of 7-bromo-7-chloronorcarane proceeded with a lower degree of stereospecificity. Analogous results have very recently been reported by Altman and Baldwin.[5] Obviously, this

TABLE II

Reduction of Halide III with Tri-n-butyltin Hydride

Compd	Temp °C	Time hr	Yield %	Isomer ratio c : d
IIIa	-20	5	71	81 : 19
	0	3	75	79 : 21
	80	2	86	74 : 26
IIIb	-20	5	73	63 : 37
	0	3	79	69 : 31
	80	2	80	73 : 27

indicates that the inversion of configuration of the 7-chloro-7-norcaryl radical takes place at a rate comparable to its hydrogen abstraction at 0° or below, and at a rate faster than the latter at 80°.

From the results described above, it can be concluded that the α-methyl- and the α-phenylcyclopropyl radicals are configurationally less stable than the corresponding chloro radical, and the α-methyl and the α-phenyl substituents do not have the ability of stabilizing the pyramidal structure of the cyclopropyl radical.

EXPERIMENTAL SECTION

GENERAL. All boiling and melting points are uncorrected. Infrared spectra were recorded on a Shimadzu IR-27 infrared spectrometer. Proton NMR spectra were measured with Varian Associates T-60 and EM-360 spectrometers (60 MHz) for solutions in carbon tetrachloride with tetramethylsilane (Me_4Si) as an internal standard. The chemical shifts are expressed in parts per million downfield from Me_4Si. Mass spectra were taken on a Hitachi RMS-4 mass spectrometer at an ionizing potential of 70 eV. Gas chromatographic (GLC) analyses were carried out with Shimadzu GC-2C and GC-6A gas chromatographs. Isomer distributions were calculated from the peak areas in gas chromatograms. The accuracy for the values of the isomer ratios listed in Tables I and II is within ±2%.

MATERIALS. All reagents were commercially available and

were used without further purification. Solvents were distilled prior to use.

exo-7-CHLORO-endo-7-METHYLNORCARANE (Ia). To a solution of 33g (0.2 mol) of 7,7-dichloronorcarane in 200 ml of tetrahydrofuran was added, under nitrogen atmosphere, 250 ml of a 0.8N solution of n-butyllithium in n-hexane at -75 to -80°. After the addition was over, the reaction mixture was stirred at -85° for 2 hr, and then an excess of methyl iodide was slowly added. The mixture was warmed up to room temperature, poured onto ice water, and was worked up as usual. The organic fraction was distilled under reduced pressure to give 7.6g of exo-7-chloro-endo-7-methylnorcarane (Ia) as a colorless liquid: 22% yield; bp 80.0-83.0° (35 mm); n_D^{20} 1.4822; ir (film) 2950 (s), 2865 (m), 1466 (m), 1169 (m), 1069 (m), 747 cm^{-1} (w); ^1H NMR δ 0.7-2.6 (complex m, 10H) and 1.70 (s, 3H); mass spectrum m/e (rel. abundance) 146 (P+2, 3), 144 (P, 9), 109 (72), 102 (29), 81 (63), 79 (27), 68 (66), 67 (100).

endo-7-CHLORO-exo-7-METHYLNORCARANE (Ib). Methylation described above was conducted at -120 to -110° to give a mixture of isomers (exo Me : endo Me = 71 : 29) in 29% yield. Preparative GLC separation on this isomeric mixture afforded endo-7-chloro-exo-7-methylnorcarane (Ib), more than 99% pure: n_D^{23} 1.4836; ir (film) 2948 (s), 2862 (m), 1445 (m), 1170 (m), 1076 (m), 796 cm^{-1} (m); ^1H NMR δ 0.7-2.6 (complex m, 10H) and 1.71 (s, 3H); mass spectrum m/e (rel. abundance) 146 (P+2, 3), 144 (P, 9), 109 (60), 102 (37), 81 (65), 79 (29), 68 (63), 67 (100).

7-CHLORO-7-PHENYLNORCARANE (IIa AND IIb) was prepared

from the addition of chlorophenylcarbene, generated by the reaction of benzal chloride with potassium tert-butoxide,[11] to cyclohexene in 58% yield: bp 96.0-98.0° (1.0 mm) (lit. 170-173° at 33 mm[11a]); n_D^{23} 1.5559 (lit. n_D^{31} 1.5562[11a]); ir (film) 3020 (s), 2924 (vs), 2880 (s), 1600 (m), 1492 (s), 1444 (vs), 1175 (m), 1075 (m), 970 (m), 745 (vs), 698 cm^{-1} (vs); ^1H NMR δ 0.2-2.3 (complex m, 10H) and 6.9-7.6 (m, 5H).

endo-7-CHLORO-exo-7-PHENYLNORCARANE (IIb). A mixture of 60g (0.3 mol) of 7-chloro-7-phenylnorcarane (mixture of isomers) and 25.5g (0.15 mol) of silver nitrate in 200 ml of methanol was stirred at room temperature for 24 hr. After the reaction mixture was filtered to remove the precipitates, water and ether were added to the filtrate. The organic layer was separated and was worked up as usual. Column chromatography on silica gel (Wakogel C-200) and elution with ligroin gave only one isomer IIb as a colorless solid: mp 35.0-36.5° (lit. 36-37°[12]); ir (film) 3020 (w), 2950 (s), 2880 (m), 1603 (w), 1498 (m), 1445 (s), 1020 (m), 755 (s), 738 (s), 697 cm^{-1} (s); ^1H NMR δ 1.0-2.3 (complex m, 10H) and 7.0-7.5 (m, 5H); mass spectrum m/e (rel. abundance) 208 (P+2, 10), 206 (P, 30), 171 (31), 138 (100), 129 (59), 115 (30), 103 (31), 91 (27), 77 (13).

exo-7-BROMO-endo-7-CHLORONORCARANE (IIIa). Isomeric mixture (endo Cl : exo Cl = 47 : 53) of 7-bromo-7-chloronorcarane was prepared according to the reported method.[4] A solution of 20g (0.1 mol) of 7-bromo-7-chloronorcarane in 100 ml of quinoline was stirred at 140° for 24 hr, and was distilled under reduced pressure to collect crude volatile

materials. The crude products were redistilled in vacuo to give only a pure isomer IIIa: bp 71.0-72.0° (6 mm); n_D^{22} 1.5289; ir (film) 2940 (vs), 2865 (s), 1465 (m), 1445 (s), 1335 (m), 1165 (m), 1093 (m), 1081 (m), 1023 (s), 967 (m), 830 (m), 765 (s), 742 cm^{-1} (s); mass spectrum m/e (rel. abundance) 212 (P+4, 1), 210 (P+2, 4), 208 (P, 3), 170 (6), 168 (24), 166 (18), 157 (1), 155 (4), 153 (3), 131 (5), 129 (15), 93 (20), 68 (100).

endo-7-BROMO-exo-7-CHLORONORCARANE (IIIb) was prepared from the bromination of 7-chloro-7-norcaryllithium at -80° according to the literature procedure:[9] 11% yield; bp 76.0-77.0° (5 mm); n_D^{28} 1.5247; ir (film) 2950 (vs), 2865 (s), 1464 (m), 1448 (s), 1337 (m), 1165 (m), 1083 (m), 1023 (s), 968 (m), 838 (m), 827 (m), 782 (m), 768 cm^{-1} (s); mass spectrum m/e (rel. abundance) 212 (P+4, 0.4), 210 (P+2, 2), 208 (P, 1), 170 (6), 168 (22), 166 (16), 157 (1), 155 (4), 153 (3), 131 (4), 129 (13), 93 (18), 68 (100).

REDUCTION OF HALIDES (I, II, AND III) WITH TRI-n-BUTYLTIN HYDRIDE. In a 10-ml flask fitted with a magnetic stirrer, a thermometer, an inlet tube for nitrogen, and a rubber septum for a syringe was placed 5-10 mmol of the halide and, if necessary, a catalytic amount of azobisisobutyronitrile (AIBN) or di-tert-butyl peroxide (DTBP). To this mixture was added under nitrogen atmosphere 1.2 equiv of tri-n-butyltin hydride by use of a syringe at a constant temperature. After the reaction was over, the reaction mixture was submitted to GLC before distillation and the isomer ratios were determined.

7-METHYLNORCARANE (IVc AND IVd): bp 62.0-63.0° (55 mm)

(lit. 123-125° at 750 mm[13]); n_D^{20} 1.4614 (lit. n_D^{26} 1.4496[13]); ir (film) 3000 (m), 2930 (s), 2860 (m), 1448 (m), 1176 (m), 1015 (w), 744 cm^{-1} (m); ^1H NMR δ 0.4-2.4 (complex m, 11H) and 0.94 (d, 3H, J = 4.0 Hz) for IVc, 0.2-2.3 (complex m, 11H) and 1.00 (d, 3H, J = 5.2 Hz) for IVd; mass spectrum m/e (rel. abundance) 110 (P, 31), 95 (31), 81 (100), 79 (18), 69 (20), 67 (75) for IVc, 110 (P, 43), 95 (31), 81 (100), 79 (23), 69 (20), 67 (82) for IVd.

7-PHENYLNORCARANE (Vc AND Vd): bp 72.0-73.0° (0.5 mm) (lit. 127-128° at 13 mm[11a]); n_D^{25} 1.5430 (lit. n_D^{24} 1.5524[11a]); ir (film) 3020 (m), 2950 (s), 2880 (m), 1604 (w), 1495 (m), 1452 (m), 1070 (m), 1025 (m), 776 (s), 717 (s), 700 cm^{-1} (s); ^1H NMR δ 0.4-2.3 (complex m, 11H) and 7.17 (broad s, 5H) for Vc, 0.7-2.6 (complex m, 11H) and 6.7-7.3 (m, 5H) for Vd; mass spectrum m/e (rel. abundance) 172 (P, 68), 130 (26), 129 (48), 128 (26), 117 (26), 115 (30), 103 (90), 91 (56), 81 (100), 80 (50), 79 (28) for Vc, 172 (P, 76), 130 (30), 129 (50), 128 (26), 117 (30), 115 (30), 104 (100), 91 (55), 81 (87), 80 (42), 79 (24) for Vd.

7-CHLORONORCARANE (VIc AND VId): bp 60.0-62.0° (13 mm) (lit. 56-58° at 11 mm[14]); n_D^{26} 1.4853 (lit. n_D^{25} 1.4861[14]); ir (film) 3000 (m), 2936 (s), 2860 (s), 1446 (m), 1285 (m), 1063 (w), 1010 (w), 723 (m), 685 cm^{-1} (m); ^1H NMR δ 0.7-2.3 (complex m, 10H) and 3.14 (t, 1H, J = 7.6 Hz) for VIc, 0.8-2.3 (complex m, 10H) and 2.58 (t, 1H, J = 3.4 Hz) for VId; mass spectrum m/e (rel. abundance) 132 (P+2, 5), 130 (P, 15), 117 (0.3), 115 (0.9), 104 (2), 103 (5), 102 (1), 101 (3), 95 (53), 90 (22), 88 (66), 81 (100), 67 (53).

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Chapter 4

BROMINATIVE DECARBOXYLATION OF 1-SUBSTITUTED 2,2-DICHLORO-3-METHYLCYCLOPROPANECARBOXYLIC ACIDS

The brominative decarboxylation of (Z)- and (E)-1-methoxy-2,2-dichloro-3-methylcyclopropanecarboxylic acids in carbon tetrachloride at 0 and 77° has been found to occur with substantial inversion of configuration, suggesting the low configurational stability of the α-methoxycyclopropyl radical as compared with the α-methoxyvinyl radical.

Recent studies on reactions which proceed via α-substituted cyclopropyl radicals, e. g., the Hunsdiecker reaction of α-substituted cyclopropanecarboxylic acids,[1] the reduction of α-substituted cyclopropyl halides with organotin hydride,[2-4] and the thermal or photolytic decomposition of α-substituted cyclopropanepercarboxylic acid esters,[1,5] have revealed the profound effect of α substituents on the configurational stability of α-substituted cyclopropyl radicals.

The substituents hitherto examined are, however, rather

limited and include only fluoro,[1,2a,2b,2d] chloro,[1,2b,3b,4,5] trifluoromethyl,[3a] methoxycarbonyl,[2c] and cyano.[2c] The aim of the present study is to generate the α-methoxycyclopropyl radical, which seems to have escaped the investigation because of its synthetic difficulty, by use of the brominative decarboxylation and to compare its configurational stability with those of other related radicals.

RESULTS AND DISCUSSION

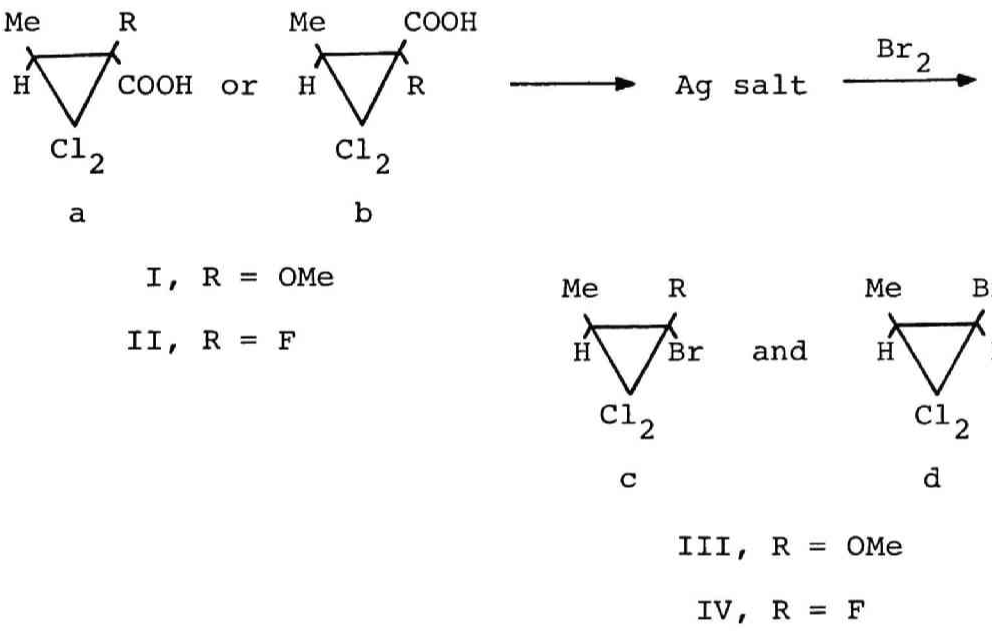
Methyl (Z)-α-methoxycrotonate was obtained by the reaction of methyl 2,3-dibromobutyrate with sodium methoxide in methanol.[6] The Z stereochemistry was assigned to the methyl ester on the basis of the chemical shift of the vinyl proton (δ 6.13; calcd, 5.67[7]). Methyl (E)-α-methoxycrotonate was prepared from the corresponding glycidate as a starting material by the method described in the Experimental Section. None of the other preparations tried were satisfactory.[8] The E assignment to the ester was based on good agreement of the observed chemical shift of the vinyl proton with the calculated one (δ 5.14; calcd, 5.18[7]). Methyl (Z)-α-fluorocrotonate was prepared according to the procedure of Shahak[9] with a slight modification. The corresponding E-fluoro ester could not be obtained by any methods. The Z configuration of methyl α-fluorocrotonate was tentatively assigned to the product based on both the chemical shift and the vicinal coupling with fluorine of the vinyl proton, i. e., δ 6.15

(calcd, 5.86[7]) and J_{HF} = 33.0 Hz, respectively. (Z)- and (E)-1-Methoxy-, and (Z)-1-fluoro-2,2-dichloro-3-methylcyclopropanecarboxylic acids (Ia, Ib, and IIa) were obtained as a crystalline solid by the addition of dichlorocarbene, generated from thermal decomposition of sodium trichloroacetate, to the corresponding methyl crotonate followed by alkaline hydrolysis. The physical and spectral data of these free acids were in good accord with the proposed structures.

The brominative decarboxylation of the acids was effected by adding an equivalent amount of bromine to a suspension of the silver salt in carbon tetrachloride either at 0° or at 77°, and keeping the reaction mixture at the same temperature for 0.5-3.0 hr, followed by a usual work-up. The isomer distributions in the resulting bromides were determined by GLC prior to distillation and are listed in Tables I and II, together with the reaction conditions. The values of the isomer ratios are accurate within ±2%. The geometrical configurations of IIIc and IIId were determined by comparing the rates of their ring opening in hot quinoline;[10] when a sample of the product obtained from the Hunsdiecker reaction at 0° was heated in quinoline at 110°, the isomer ratio changed from 56/44 to 44/56 (after 1 hr) and to 28/72 (after 2 hr). According to the Woodward-Hoffmann-DePuy's rule,[11] structure IIIc should be assigned to the more readily decomposing isomer. The structural assignment to the isomers, IVc and IVd, was made from their proton NMR spectra, based on the generalization[12] that in fluorocyclopropanes the ring hydrogen is more strongly coupled with cis than with trans fluorine.

Thus, the vicinal coupling constants of ring hydrogen with fluorine were 7.2 Hz for IVc and 19.8 Hz for IVd.

SCHEME



As is shown in Table I, the brominative decarboxylation of acids Ia and Ib occurred with substantial inversion of configuration of the starting acids even at 0°, and the ratio of retention to inversion decreased as the reaction temperature increased. At 77°, the ratio was essentially the same irrespective of the stereochemistry of the initial cyclopropanecarboxylic acid. This means that the α-methoxycyclopropyl radical is configurationally rather unstable and the rate

of inversion of its configuration is comparable to that of its bromine abstraction at 0°, and is faster than that of the latter at 77°. The behavior of the α-methoxycyclopropyl radical described herein is in sharp contrast with those of the (Z)- and (E)-1-methoxy-1-propenyl radicals, both of which have been reported[13] to be configurationally stable enough to retain their configurations even in the thermal decomposition of the corresponding percarboxylic acid esters in protonic media at 110°. This difference must be ascribed, at

TABLE I

Hunsdiecker Reaction of Ia and Ib

Compd	Temp °C	Time hr	Yield %	Isomer ratio retn : invn
Ia	0	1.5	54	58 : 42
		2.0	76	56 : 44
	77	1.5	53	41 : 59
		2.0	59	39 : 61
Ib	0	2.0		68 : 32
		3.0	71	69 : 31
	77	0.5		61 : 39
		1.0	62	62 : 38

least partly, to the difference in the s character of the odd-electron orbital between the cyclopropyl and the vinyl systems. It seems to be noted, in this connection, that a similar difference has been observed between the α-chlorocyclopropyl[1] and the α-chlorovinyl radicals.[14]

TABLE II

Hunsdiecker Reaction of Acid IIa

Temp °C	Time hr	Yield %	Isomer ratio retn : invn
20	1.5		90 : 10
	2.5	59	91 : 9
77	2.0	69	81 : 19
	3.0		82 : 18

In the system of the present study, two chlorine atoms are situated at the position β to the radical center. The possible effect of electronegative β-substituents on the configurational stability of the intermediary radical could not be disregarded, because the presence of chlorine atoms at the 2 position may cause the destabilization of its pyramidal structure relative to its planar one.

In this point of view, the results of the brominative

decarboxylation of (Z)-1-fluoro-2,2-dichloro-3-methylcyclopropanecarboxylic acid (IIa) are very suggestive. Table II demonstrates that the reaction occurred with a considerable extent of inversion of configuration even at room temperature. This strongly suggests the decrease of the configurational stability of the intermediately formed α-fluorocyclopropyl radical, which is one of the configurationally most stable radicals ever known,[1,2a,b] by the presence of two chlorine atoms at the 2 position. The remote substituent effect of this type, which was suggested by Bingham and Dewar[15] from the theoretical studies and was demonstrated with the previous work[16] on the reduction of 1-substituted 7-halo-7-fluoronorcaranes with tri-n-butyltin hydride, will be discussed in detail in Part II.

EXPERIMENTAL SECTION[17]

METHYL (Z)-α-METHOXYCROTONATE was prepared according to the method of Owen.[6]

METHYL (E)-α-METHOXYCROTONATE. A solution of methyl trans-2-methylglycidate (0.13 mol), prepared from methyl trans-crotonate and m-chloroperbenzoic acid in dichloromethane, and p-toluenesulfonic acid (0.13 mol) in 100 ml of dry ether was constantly stirred at room temperature for 40 hr. The solvent was evaporated in vacuo to give a colorless oil (100%): ir (film) 3480 (m), 1748 (vs), 1600 (m), 1359 (s), 1193 (s), 1178 cm^{-1} (vs); ^1H NMR (chloroform-d) δ 1.28 (d, 3H,

$\underline{J}$ = 6.6 Hz), 2.49 (s, 3H), 3.86 (s, 3H), 4.39 (m, 1H), 4.86 (broad s, 1H), 4.92 (m, 1H), and 7.67 (m, 4H). The crude product, methyl α-hydroxy-β-$\underline{p}$-toluenesulfonyloxybutyrate, (0.13 mol) was dissolved in 50 ml of methyl iodide and cooled in an ice bath. To this solution was gradually added silver oxide (0.13 mol) in small portions so that the temperature did not rise over 10°. After the addition was complete, the mixture was stirred at room temperature for 20 hr. The solid was removed by filtration and washed with ether. The ethereal filtrates were concentrated under reduced pressure to dryness to give a pale yellow liquid (97%): ir (film) 1753 (s), 1599 (m), 1364 (s), 1189 (s), 1177 (s), 1080 cm^{-1} (m); ^1H NMR δ 1.18 (d, 3H, $\underline{J}$ = 6.6 Hz), 2.45 (s, 3H), 3.34 (s, 3H), 3.64 (s, 3H), 3.77 (m, 1H), 4.72 (m, 1H), and 7.46 (m, 4H). This methylated ester was used without further purification. To a solution of potassium hydroxide (0.35 mol) in 100 ml of anhydrous methanol was added dropwise a solution of methyl α-methoxy-β-$\underline{p}$-toluenesulfonyloxybutyrate (0.12 mol) in 50 ml of anhydrous methanol. White precipitates appeared immediately. After the reaction mixture was stirred at room temperature for 20 hr, the precipitates were filtered off and washed with a small amount of anhydrous methanol. The filtrates were concentrated under reduced pressure, diluted with water, made acidic with hydrochloric acid, and extracted four times with 50 ml of ether. The ethereal extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to give an isomeric mixture (E acid : Z acid = 85 : 15 from NMR) of α-methoxycrotonic acid. The isomeric mixture was recrystal-

lized from n-hexane to afford white needles of pure (E)-α-methoxycrotonic acid (65%): mp 44.5-45.5°; ir (KBr) 3010 (m), 1705 (vs), 1636 (m), 1211 (s), 1179 cm^{-1} (s); ^1H NMR (chloroform-d) δ 2.09 (d, 3H, J = 7.4 Hz), 3.67 (s, 3H), 5.57 (q, 1H, J = 7.4 Hz), and 10.77 (broad s, 1H). The acid thus obtained was converted to the methyl ester by a conventional method of methyl iodide-silver oxide combination (82%): bp 62.0-63.0° (16 mm); n_D^{21} 1.4358; ir (film) 1727 (vs), 1644 (m), 1441 (s), 1369 (s), 1253 (vs), 1207 (vs), 1164 (vs), 1105 (s), 1026 cm^{-1} (s); ^1H NMR δ 1.93 (d, 3H, J = 7.4 Hz), 3.50 (s, 3H), 3.70 (s, 3H), and 5.14 (q, 1H, J = 7.4 Hz); mass spectrum m/e (rel. abundance) 130 (P, 68), 115 (52), 99 (19), 71 (65), 59 (61), 55 (100).

METHYL (Z)-α-FLUOROCROTONATE was prepared as follows. Methyl oxalate (0.44 mol) and methyl fluoroacetate (0.02 mol) were added with stirring to a suspension of sodium hydride (0.42 mol) in 200 ml of dry tetrahydrofuran. After the reaction had been initiated by refluxing, the balance of the fluorinated ester (0.38 mol) was slowly added to the mixture at 40-45° and the whole was heated at 60° for 3 hr. To it was added freshly distilled acetaldehyde (0.41 mol) at 0°, and the mixture was slowly brought to refluxing at which it was maintained for 1 hr. The reaction mixture was poured into water and the resulting solution was extracted three times with 50 ml of dichloromethane. The organic extracts were washed with 5% sodium carbonate and with water, dried over anhydrous sodium sulfate, and distilled to give a colorless liquid (61%): bp 121.0-123.0°; n_D^{24} 1.4085; ir (film)

1740 (vs), 1683 (s), 1438 (s), 1346 (s), 1328 (s), 1280 (vs), 1175 (vs), 1103 (vs), 855 cm^{-1} (m); ^1H NMR δ 1.77 (dd, 3H, J = 7.2 and 2.4 Hz), 3.78 (s, 3H), and 6.15 (dq, 1H, J = 7.2 and 33.0 Hz); mass spectrum m/e (rel. abundance) 118 (P, 82), 103 (16), 87 (100), 59 (92).

PREPARATION OF 1-SUBSTITUTED 2,2-DICHLORO-3-METHYLCYCLOPROPANECARBOXYLIC ACIDS (I AND II). As a typical one, preparation of (E)-1-methoxy-2,2-dichloro-3-methylcyclopropanecarboxylic acid (Ib) is described below. A solution of methyl (E)-α-methoxycrotonate (0.12 mol) in 100 ml of dry 1,2-dimethoxyethane was heated to reflux with stirring, and to it was added gradually sodium trichloroacetate (0.18 mol) in small portions. After the addition was over, the mixture was allowed to reflux for 15 hr with stirring. The reaction mixture was cooled to room temperature, and poured into water, and the resultant mixture was extracted three times with ether. The ethereal extracts were dried over anhydrous sodium sulfate, filtered, and distilled *in vacuo* to yield a colorless liquid (45%). The cyclopropanecarboxylic acid methyl ester obtained was hydrolyzed with 1.5 equiv of potassium hydroxide in 100 ml of 50% aqueous ethanol to the free acid, which was recrystallized from n-hexane to give white needles (81%): mp 52.5-53.5°; ir (KBr) 3030 (s), 1706 (vs), 1301 (vs), 1158 (m), 1075 cm^{-1} (m); ^1H NMR δ 1.43 (d, 3H, J = 6.6 Hz), 2.03 (q, 1H, J = 6.6 Hz), 3.61 (s, 3H), and 12.14 (s, 1H).

Anal. Calcd for $C_6H_8O_3Cl_2$: C, 36.21; H, 4.05. Found: C, 36.29; H, 4.32.

(Z)-1-METHOXY-2,2-DICHLORO-3-METHYLCYCLOPROPANECARBOXYLIC ACID (Ia) was obtained in an overall yield of 37%: mp 75.0-76.0° (from n-hexane); ir (KBr) 3000 (s), 1708 (vs), 1292 (s), 1253 (s), 1040 cm^{-1} (s); ^1H NMR δ 1.29 (d, 3H, J = 6.6 Hz), 2.43 (q, 1H, J = 6.6 Hz), 3.76 (s, 3H), and 12.24 (s, 1H).

Anal. Calcd for $C_6H_8O_3Cl_2$: C, 36.21; H, 4.05; Cl, 35.63. Found: C, 36.30; H, 4.11; Cl, 35.47.

(Z)-1-FLUORO-2,2-DICHLORO-3-METHYLCYCLOPROPANECARBOXYLIC ACID (IIa) was obtained in an overall yield of 32%: mp 42.0-43.0° (from petroleum ether); ir (KBr) 3000 (m), 1720 (vs), 1250 (vs), 1180 (s), 1000 cm^{-1} (s); ^1H NMR δ 1.37 (d, 3H, J = 6.6 Hz), 2.53 (dq, 1H, J = 6.6 and 7.8 Hz), and 11.14 (s, 1H).

Anal. Calcd for $C_5H_5O_2Cl_2F$: C, 32.11; H, 2.70; Cl, 37.92; F, 10.16. Found: C, 31.82; H, 2.57; Cl, 38.04; F, 10.16.

BROMINATIVE DECARBOXYLATION OF ACIDS (Ia, Ib, AND IIa). In a 50-ml three-necked flask equipped with a thermometer, a dropping funnel, a stirrer bar, and a condenser with a drying tube at the top was placed the silver salt (5 mmol) and 10 ml of dry carbon tetrachloride. To this stirred suspension kept at a specified temperature was rapidly added 1.2 equiv of bromine in 10 ml of dry carbon tetrachloride. After being kept at the same temperature for several hours, the reaction mixture was allowed to stand at room temperature. Inorganic silver salts were removed by filtration and washed with a small amount of carbon tetrachloride. The filtrates were concentrated by rotary evaporation below 30°. The residue was carefully distilled under reduced pressure. The isomer

compositions of the products were determined by GLC before distillation and are shown in Tables I and II.

IIIc and IIId: bp 78.0-79.0° (15 mm); n_D^{20} 1.4869; ir (film) 2960 (m), 1043 (s), 780 (vs), 765 cm^{-1} (vs); ^1H NMR δ 1.30 (d, 3H, J = 6.6 Hz), 2.12 (q, 1H, J = 6.6 Hz), and 3.54 (s, 3H) for IIIc, 1.25 (d, 3H, J = 6.6 Hz), 1.84 (q, 1H, J = 6.6 Hz), and 3.54 (s, 3H) for IIId; mass spectrum m/e (rel. abundance) 232 (P, 1), 217 (5), 201 (28), 199 (100), 197 (79), 153 (51), 109 (26), 107 (23), 105 (20), 103 (48).

IVc and IVd: bp 52.0-53.0° (23 mm); n_D^{27} 1.4779; ir (film) 2940 (w), 1069 (m), 996 (s), 898 (s), 862 cm^{-1} (s); ^1H NMR δ 1.35 (d, 3H, J = 6.6 Hz) and 2.03 (dq, 1H, J = 6.6 and 7.2 Hz) for IVc, 1.33 (dd, 3H, J = 6.6 and 1.6 Hz) and 2.06 (dq, 1H, J = 6.6 and 19.8 Hz) for IVd; mass spectrum m/e (rel. abundance) no parent peak to 220, 205 (6), 192 (6), 185 (10), 141 (100), 121 (17), 105 (72), 85 (52).

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Chapter 5

REDUCTION OF 1-SUBSTITUTED 2,2-DICHLORO-3-METHYLCYCLOPROPYL BROMIDES WITH TRI-n-BUTYLTIN HYDRIDE

1-Fluoro- (I), 1-phenoxy- (II), 1-methoxy- (III), and 1,2,2-trichloro-3-methylcyclopropyl bromides (IV) were synthesized as an isomeric mixture and were separately reduced with tri-n-butyltin hydride at various temperature in order to examine the stereochemistry of their reactions. The stereospecificity observed in these reactions was found to decrease in the order: I > II > III > IV, which suggests that the effect of these α substituents of stabilizing the pyramidal structure of cyclopropyl radicals decreases in the order: fluoro > phenoxy > methoxy > chloro. This order in the stabilizing effect is closely related to the electronegativity of the α substituents.

Much attention has been focussed on the role of the substituent α to the radical center in stabilizing the configuration of a cyclopropyl radical. The degree of its configur-

ational stability has been found to be profoundly affected by the nature of the α substituent.[1-9] Thus, it has been reported[4] very recently that the brominative decarboxylation of 7-fluoronorcarane-7-carboxylic acid and the thermal decomposition of its peroxy ester proceeded with extremely high stereospecificity, whereas the reactions involving the corresponding chloro radical took place with fairly high to little or no stereospecificity. These observations were explained in terms of the electronic effect, or the electronegativity effect, of the α substituents.

In order to obtain further information about this problem, a study has now been made on the stereochemistry of the reduction of 1-substituted 2,2-dichloro-3-methylcyclopropyl bromides with tri-n-butyltin hydride.

RESULTS

Methyl (Z)-α-fluorocrotonate was prepared by the condensation of methyl fluoroacetate with acetaldehyde. Its configuration was determined by ^{1}H NMR spectroscopy on the basis of the generalization[10] that in 1-fluorovinyl systems fluorine is more strongly coupled with trans proton than with cis proton. Methyl (Z)-α-methoxycrotonate was obtained according to the method of Owen.[11] Methyl (Z)-α-phenoxy- and (Z)-α-chlorocrotonate were prepared by treating methyl 2,3-dibromobutanoate with sodium phenoxide in tetrahydrofuran and methyl 2,3-dichlorobutanoate with triethylamine, respectively. The

chemical shift for the vinyl proton in the chloro ester (δ 6.90) calculated from Pascual-Simon's table[12] was in good agreement with the observed value (δ 7.05), the difference being within a standard deviation of 0.17 ppm associated with the additivity calculation. This method was not effective for the stereochemical assignment to the phenoxy ester, since the observed value (δ 6.62) was too far from the calculated values for either of the isomers (δ 5.82 for the Z configuration and 5.63 for the E configuration). In order to obtain further information of their stereochemical arrangements, (Z)-β-phenoxy- and (Z)-β-chlorocrotyl alcohols were prepared by the reduction of these two esters with lithium aluminun hydride, and the induced shifts in their ^{1}H NMR spectra were measured with successive addition of tris(dipivaloylmethanato)-europium, Eu(dpm)$_3$, up to the molar ratio of 4.0×10^{-2} ([Eu(dpm)$_3$]/[alcohol]). As shown in Figure I, good straight lines were obtained on plotting the induced shifts against the molar ratios of Eu(dpm)$_3$ to the alcohol. Every couple of lines for the protons located at the same positions in both alcohols has a parallel relationship. This means that these two alcohols have the same configuration. The fact that the shift gradient for the vinyl proton is more than twice as large as the one for the methyl proton substantiates the proposed assignment of stereochemistry, because the observed shifts can be best rationalized by the assignment of the Z configuration to the alcohols.

The addition of dichlorocarbene to these methyl esters followed by alkaline hydrolysis gave the corresponding cyclo-

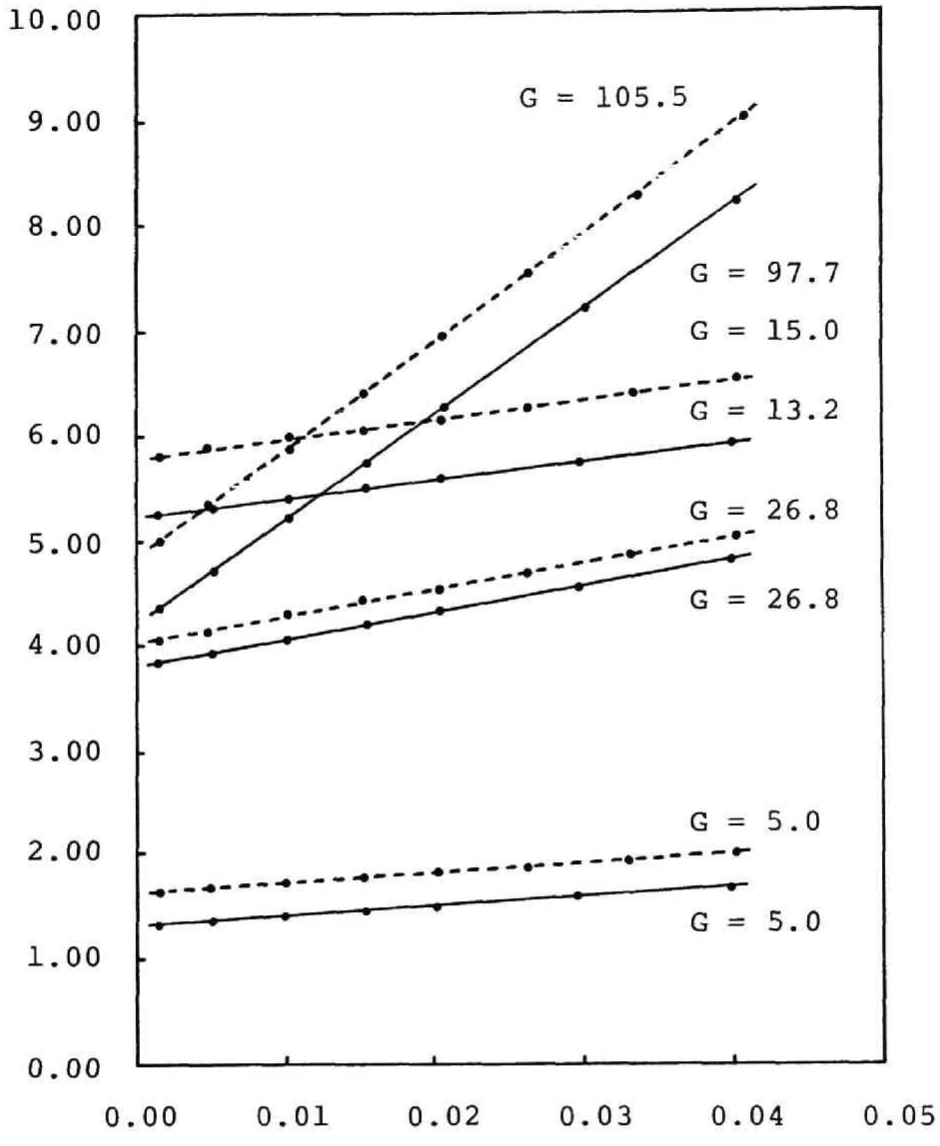
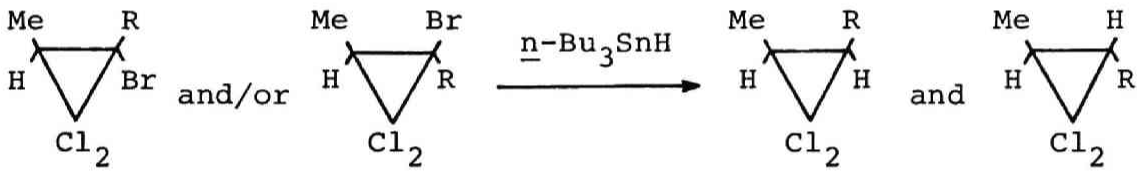


FIGURE I. Plot of Induced Chemical Shifts against Molar Ratios of $Eu(dpm)_3$ to Alcohol

Solid and dotted lines denote the plots for (Z)-β-phenoxy- and (Z)-β-chlorocrotyl alcohols, respectively.

propanecarboxylic acids in fairly good yields. The free acids thus obtained were subject to the Hunsdiecker or the Kochi reaction to afford cyclopropyl bromides (I, II, III, and IV) as an isomeric mixture. By means of preparative GLC the bromides except IV were separated into E (isomer a) and Z (isomer b) isomers. All attempts to separate the isomers of IV by preparative GLC were unsuccessful, but only one isomer was obtained from thermal decomposition of an isomeric mixture.

SCHEME



a b c d

I, R = F

II, R = OPh

III, R = OMe

IV, R = Cl

V, R = F

VI, R = OPh

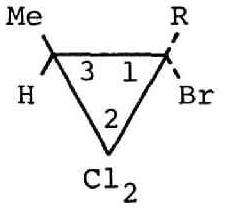
VII, R = OMe

VIII, R = Cl

Carbon-13 NMR study allowed the assignment of stereochemistry to these bromides. ^{13}C NMR data are summarized in Table I. It has been well documented[13] that the γ gauche effect, i. e., the upfield shift observed for the resonance of a carbon which

TABLE I

^{13}C NMR Data for 1-Substituted 2,2-Dichloro-3-methylcyclopropyl Bromides



R	Cl		OMe		OPh		F	
Configuration	E	Z	E	Z	E	Z	E (J_{CF}, Hz)	Z (J_{CF}, Hz)
C-1	53.5	53.5	87.7	87.7	80.4	80.4	137.8(532.9)	137.8(532.9)
C-2	56.8	56.8	82.0	82.0	74.1	74.1	83.9(313.7)	89.9(315.4)
C-3	41.0	40.5	41.5	38.2	40.4	37.6	39.7(12.1)	37.1(10.4)
C-Me	10.9	13.6	8.1	13.3	8.5	13.2	7.9(5.2)	12.7(0)
C-R			57.8	57.8	154.1	154.7		
o					117.0	117.0		
m					129.2	129.2		
p					123.4	123.4		

is gauche (or cis) to another carbon or a hetero substituent at the γ position, is of particular utility for stereochemical assignment. The magnitude of the γ anti effect, i. e., the upfield shift caused by the substituent at the γ anti (or trans) position, is in the range of 0.5-2.5 ppm, being much smaller than that of the γ gauche effect of the same substituent. This means that in these systems configurational assignment can be made from the chemical shift of the methyl carbon; the larger the γ gauche effect of the substituent cis to the methyl is, the larger the chemical shift of the methyl carbon must be. Since the γ gauche effect of bromine is known to be smaller than any of the four substituents, i. e., fluoro, phenoxy, methoxy, and chloro,[14] it has been concluded that in these epimeric (E)- and (Z)-1-substituted 2,2-dichloro-3-methylcyclopropyl bromides the one that has a larger chemical shift for methyl carbon has the Z configuration and the other that has a smaller one corresponds to the E stereochemistry. Further confirmation of this stereochemical assignment was obtained from ^{1}H NMR spectra of the fluoro compounds.

Each isomer was separately reduced with tri-n-butyltin hydride at various temperature by either of two methods (Methods A and B). The isomer distributions in the products were determined by GLC and/or ^{1}H NMR analyses. Assignment of configuration to the products (c and d) was made from their ^{1}H NMR spectra on the basis of the well-established geometrical dependence of vicinal proton-proton couplings.[10] The results are compiled in Table II, together with the reac-

tion conditions.

DISCUSSION

The reduction of 1,2,2-trichloro-3-methylcyclopropyl bromide (IVa and IVb) with tri-n-butyltin hydride occurred non-stereospecifically, whereas that of 1-fluoro-2,2-dichloro-3-methylcyclopropyl bromide (Ia and Ib) proceeded with much retention of configuration (Table II). This means that the α-chlorocyclopropyl radical inverts its configuration much faster than its hydrogen abstraction from the tin hydride and that the α-fluorocyclopropyl radical is configurationally so stable that its hydrogen abstraction takes precedence over its configurational inversion. The stereospecificity observed with the fluoro compound, however, is lower than that observed in the reduction of 7-chloro-7-fluoronorcarane with tri-n-butyltin hydride.[2] This can be ascribed to the presence of chlorine atoms at the position β to the radical center, as reported very recently by Ando and co-workers.[15] Bingham and Dewar[16] also suggested from the theoretical point of view that the β substituents play an important role in determining the configurational stability of vinyl and cyclopropyl radicals. Their theoretical studies lead to the expectation that 1-alkoxy-2,2-dichloro-3-methylcyclopropyl bromides should be reduced with little or no retention of configuration. As is shown in Table II, the reduction of 1-phenoxy- (II) and 1-methoxy-2,2-dichloro-3-methylcyclopropyl bromide (III) pro-

TABLE II

Reduction of Cyclopropyl Bromides (I, II, III, and IV)

Compd	Mol ratio compd : SnH	Temp °C	Time hr	Isomer ratio c : d	Method
Ia	1 : 1.5	0	1.5	92 : 8	B
	1 : 1.5	80	1	81 : 19	B
Ib	1 : 1.5	0	1.5	10 : 90	B
	1 : 1.5	80	1	21 : 79	B
IIa	1 : 1.66	-20	3	65 : 35	A
	1 : 1.66	0	3	57 : 43	A
	1 : 1.66	40	3	52 : 48	A
	1 : 1.66	55	3	51 : 49	A
IIb	1 : 1.66	-20	3	39 : 61	A
	1 : 1.66	0	3	46 : 54	A
	1 : 1.66	40	3	49 : 51	A
	1 : 1.66	55	3	50 : 50	A

(Continued)

IIIa	1 : 4.5	-20	1	59 : 41	B
	1 : 1.5	-20	1	57 : 43	B
	1 : 1.5	0	1	54 : 46	B
IIIb	1 : 4.5	-20	1	44 : 56	B
	1 : 1.5	-20	1	45 : 55	B
	1 : 1.5	0	1	52 : 48	B
IVa	1 : 1.5	-20	3	74 : 26	A
	1 : 1.5	0	3	73 : 27	A
	1 : 1.5	40	3	71 : 29	A
IVa + IVb*	1 : 1.5	-20	3	73 : 27	A
	1 : 1.5	0	3	72 : 28	A
	1 : 1.5	40	3	72 : 28	A

* Isomer ratio, IVa : IVb = 67 : 33.

ceeded with some retention of configuration at 0° or below and at -20°, respectively. The ratio of retention to inversion decreased as the reaction temperature increased, as is the case in the brominative decarboxylation of cyclopropanecarboxylic acid silver salts and the thermal decomposition of their tert-butyl peroxy esters.[4] At 0° or above, the isomer ratios of the products are essentially the same irrespective of the stereochemistry of the starting bromides. Table II also shows that the degree of stereospecificity observed with the bromide II is slightly higher than that observed with the bromide III. These findings indicate that the α-phenoxycyclopropyl radical is configurationally more stable than the α-methoxycyclopropyl radical and their hydrogen abstraction from the tin hydride takes place at a comparative rate to inversion of their configurations.

From the above-described results, it follows that the α-fluorocyclopropyl radical is configurationally most stable, followed by the α-phenoxy- and the α-methoxycyclopropyl radical, and the α-chlorocyclopropyl radical is least stable. This order is inconsistent with that predicted by Bingham and Dewar.[16] This inconsistency, however, does not invalidate their theoretical studies, because the reduction involves the step of hydrogen abstraction by cyclopropyl radicals and the difference in the rates of hydrogen abstraction by cyclopropyl radicals should not be neglected in delicate cases.

Undoubtedly, the increase of the configurational stability, or the energy barrier for inversion, of cyclopropyl radicals can be attributed to the presence of an electronegative

α substituent. The above-cited stereochemical results lead to the conclusion that the stabilizing effect of the α substituents decreases in the order: fluoro > phenoxy > methoxy > chloro. It is noteworthy that this order is in good agreement with that of electronegativity of the substituents. This agreement affords a good support for the idea that the stabilization of the configuration of cyclopropyl radicals is primarily due to the electronegativity effect of an α substituent in origin, though at present there are no other tools available to confirm the physical basis of this effect.

On the other hand, Altman and Vederas reported[6] earlier that the α-trifluoromethyl group can not stabilize the configuration of cyclopropyl radicals. This does not invalidate the above-described argument because the electronegativity value for the trifluoromethyl group is strongly dependent on the methods of estimation[17] and appears not to be necessarily high. Moreover, the interesting fact has very recently been reported by Holmes and Thomas[18] that the trifluoromethyl group itself acts as an electron-donating group rather than an electron-attracting group to the adjacent carbon. Thus, the electronegativity of α substituents can be the best criterion for estimating the configurational stability of α-substituted cyclopropyl radicals.

EXPERIMENTAL SECTION

All boiling and melting points are uncorrected. Infrared spectra were taken on a Shimadzu IR-400 infrared spectrometer. Proton magnetic resonance spectra were measured with a Varian Associates EM-360 spectrometer (60 MHz) for solutions in carbon tetrachloride, chloroform-d, or acetone-d_6 with tetramethylsilane (Me_4Si) as an internal standard. Carbon-13 NMR spectra were recorded with a Varian Associates CFT-20 spectrometer for 0.2-0.4 mol solutions in chloroform-d with Me_4Si as an internal reference. Mass spectra were determined on a Hitachi RMS-4 mass spectrometer. Gas chromatographic analyses (GLC) and separations were done on Shimadzu GC-2C, GC-6A, and Jeolco JGC-20KT instruments.

METHYL (Z)-α-FLUOROCROTONATE. To a suspension of sodium hydride (20g, 50% dispersion in mineral oil) in 200 ml of anhydrous tetrahydrofuran was added dimethyl oxalate (51.9g, 0.44 mol) and successively methyl fluoroacetate (2g). Once the reaction started, the rest of methyl fluoroacetate (36.8g) was added slowly so as to keep the temperature at 40-50°. After the addition was complete, the reaction mixture was stirred for 3 hr at 60°. This mixture was treated with acetaldehyde (18.0g, 0.42 mol) at 0° and was refluxed for an additional hour. After the reaction was over, the mixture was poured into ice water, followed by extraction with dichloromethane. The combined extracts were washed with 5% aqueous sodium bicarbonate and with water, dried over anhydrous sodium sulfate. Distillation gave 26.2g (47%) of methyl (Z)-

α-fluorocrotonate: bp 121-123°; n_D^{24} 1.4085; ir (film) 1740 (vs), 1683 (m), 1438 (m), 1324 (m), 1270 (s), 1135 (s), 1100 (s), 760 cm^{-1} (m); ^1H NMR (CCl_4) δ 1.77 (dd, 3H, J = 7.2 and 2.4 Hz), 3.78 (s, 3H), and 6.15 (dq, 1H, J = 7.2 and 33.0 Hz); mass spectrum m/e (rel. abundance) 118 (P, 82), 103 (16), 87 (100), 59 (92).

METHYL (Z)-α-PHENOXYCROTONATE. Methyl 2,3-dibromobutanoate (130g, 0.5 mol) was slowly added to a solution of sodium phenoxide (119g, 1.0 mol) in 250 ml of anhydrous tetrahydrofuran at such a rate that the temperature was held below 10°. After the addition was over, the reaction mixture was refluxed for 38 hr, and then was allowed to cool to room temperature. The product was extracted with ether and the combined extracts were dried over anhydrous sodium sulfate. The concentrated organic layer was distilled under reduced pressure to give 73.5g (77%) of methyl (Z)-α-phenoxycrotonate: bp 132-136° (20 mm); n_D^{20} 1.5228; ir (film) 3030 (m), 2990 (s), 1730 (s), 1665 (m), 1600 (m), 1490 (m), 1428 (m), 1380 (s), 1320 (m), 1266 (s), 1217 (s), 1193 (s), 1163 (s), 1130 (s), 1064 (s), 1010 (m), 754 (s), 693 cm^{-1} (s); ^1H NMR δ 1.66 (d, 3H, J = 7.2 Hz), 3.53 (s, 3H), 6.62 (q, 1H, J = 7.2 Hz), and 7.4-6.5 (m, 5H); mass spectrum m/e (rel. abundance) 192 (P, 88), 133 (56), 105 (100), 94 (25), 77 (47).

METHYL (Z)-α-METHOXYCROTONATE was prepared according to the method of Owen.[11]

METHYL (Z)-α-CHLOROCROTONATE. To methyl 2,3-dichlorobutanoate (82.5g, 0.46 mol) was added dropwise triethylamine (55.8g, 0.55 mol) with cooling in an ice bath. After the ad-

dition was over, 50 ml of anhydrous ether was added to this mixture. It was stirred at room temperature for 16 hr. The precipitates which appeared were separated by filtration and were washed with ether. The ethereal solution thus obtained was washed with 5% hydrochloric acid until the washings become acidic, and then with water. After it was dried over anhydrous sodium sulfate, the solvent was removed. The residue was distilled under reduced pressure to afford 48.5g (79%) of methyl (Z)-α-chlorocrotonate: bp 65-70° (26 mm); n_D^{28} 1.4532; ir (film) 2950 (m), 1725 (vs), 1632 (m), 1439 (m), 1284 (vs), 1116 (m), 1045 (s), 904 (m), 777 (m), 746 cm^{-1} (s); ^1H NMR (CCl_4) δ 1.94 (d, 3H, J = 7.0 Hz), 3.77 (s, 3H), and 7.05 (q, 1H, J = 7.0 Hz).

PREPARATION OF 1-SUBSTITUTED 2,2-DICHLORO-3-METHYLCYCLOPROPANECARBOXYLIC ACIDS. Finely powdered anhydrous sodium trichloroacetate (0.3 mol) was gradually added with stirring to the ester (0.2 mol) at 130-150°. After the addition was over, the reaction mixture was stirred at the same temperature for several hours and then was poured into water. The resulting solution was subject to extraction with ether. The ethereal extracts were dried over anhydrous sodium sulfate and the solvent was evaporated in vacuo. The residual oil was distilled under reduced pressure to give cyclopropanecarboxylic acid methyl ester.

METHYL (Z)-1-FLUORO-2,2-DICHLORO-3-METHYLCYCLOPROPANECARBOXYLATE: 42% yield; bp 92.0-94.0° (19 mm); n_D^{29} 1.4578; ir (film) 2965 (m), 1740 (vs), 1440 (s), 1380 (s), 1293 (vs), 1250 (s), 1193 (s), 1155 (s), 1115 (m), 1045 (m), 1000 (s),

870 (s), 845 (s), 810 (m), 758 (m), 680 cm^{-1} (m); ^1H NMR (CCl_4) δ 1.31 (d, 3H, J = 6.6 Hz), 2.52 (dq, 1H, J = 6.6 and 7.8 Hz), and 3.88 (s, 3H); mass spectrum m/e (rel. abundance) 204 (P+4, 2), 202 (P+2, 10), 200 (P, 16), 167 (18), 165 (51), 145 (5), 143 (28), 141 (42), 137 (42), 107 (16), 105 (35), 59 (100).

METHYL (Z)-1-PHENOXY-2,2-DICHLORO-3-METHYLCYCLOPROPANE-CARBOXYLATE: 55% yield; bp 101.0-106.0° (2 mm); n_D^{17} 1.5327; ir (film) 3030 (m), 3000 (m), 1748 (vs), 1666 (m), 1600 (s), 1490 (s), 1440 (s), 1380 (m), 1280 (s), 1254 (s), 1210 (s), 1160 (s), 1093 (m), 1047 (m), 1022 (m), 864 (s), 752 (s), 696 cm^{-1} (m); ^1H NMR (CCl_4) δ 1.17 (d, 3H, J = 7.0 Hz), 2.69 (q, 1H, J = 7.0 Hz), 3.73 (s, 3H), and 6.7-7.5 (m, 5H); mass spectrum m/e (rel. abundance) 278 (P+4, 5), 276 (P+2, 24), 274 (P, 37), 241 (13), 239 (38), 219 (2), 217 (8), 215 (13), 209 (11), 207 (31), 183 (14), 181 (35), 179 (48), 105 (34), 94 (100), 77 (78).

METHYL (Z)-1-METHOXY-2,2-DICHLORO-3-METHYLCYCLOPROPANE-CARBOXYLATE: 45% yield; bp 102.0-103.0° (18 mm); n_D^{22} 1.4677; ir (film) 2955 (m), 1738 (vs), 1439 (m), 1385 (m), 1293 (vs), 1251 (s), 1205 (s), 1150 (s), 1051 (s), 1038 (s), 947 (m), 869 (m), 847 cm^{-1} (m); ^1H NMR (CCl_4) δ 1.24 (d, 3H, J = 6.6 Hz), 2.34 (q, 1H, J = 6.6 Hz), 3.63 (s, 3H), and 3.81 (s, 3H); mass spectrum m/e (rel. abundance) 216 (P+4, 2), 214 (P+2, 11), 212 (P, 17), 179 (29), 177 (86), 157 (12), 155 (70), 153 (100), 147 (26), 145 (70), 137 (25), 117 (47), 103 (36), 75 (46).

METHYL (Z)-1,2,2-TRICHLORO-3-METHYLCYCLOPROPANECARBO-

XYLATE: 54% yield; bp 102.0-107.0° (23 mm); n_D^{31} 1.4762; ir (film) 2970 (m), 1742 (vs), 1419 (m), 1265 (s), 1111 (m), 1080 (m), 921 (m), 868 (m), 785 cm^{-1} (m); ^1H NMR (CCl_4) δ 1.32 (d, 3H, J = 6.4 Hz), 2.62 (q, 1H, J = 6.4 Hz), and 3.86 (s, 3H).

Cyclopropanecarboxylic acid methyl ester thus obtained was hydrolyzed with potassium hydroxide in 50% aqueous ethanol. After a usual work-up, the acid fraction was distilled in vacuo to give crude acid, which was recrystallized from solvent.

(Z)-1-FLUORO-2,2-DICHLORO-3-METHYLCYCLOPROPANECARBOXYLIC ACID: 78% yield; bp 91.0-92.0° (1.8 mm); mp 42.0-43.0 (from petroleum ether); ir (KBr) 3700-3200 (broad s), 1720 (vs), 1440 (s), 1250 (vs), 1180 (s), 1120 (m), 1000 (s), 870 (m), 845 (m), 745 cm^{-1} (m); ^1H NMR (CCl_4) δ 1.37 (d, 3H, J = 6.6 Hz), 2.53 (dq, 1H, J = 6.6 and 7.8 Hz), and 11.14 (s, 1H).

Anal. Calcd for $C_5H_5O_2Cl_2F$: C, 32.11; H, 2.70; Cl, 37.92; F, 10.16. Found: C, 31.82; H, 2.57; Cl, 38.04; F, 10.16.

(Z)-1-PHENOXY-2,2-DICHLORO-3-METHYLCYCLOPROPANECARBOXYLIC ACID: 86% yield; mp 149.0-149.5° (from petroleum ether-benzene-ether); ir (KBr) 3125-2200 (broad s), 1725 (vs), 1689 (s), 1597 (s), 1495 (s), 1208 (s), 1179 (s), 1004 (m), 866 (m), 805 (m), 753 (s), 694 cm^{-1} (m); ^1H NMR (acetone-d_6) δ 1.14 (d, 3H, J = 6.8 Hz), 2.73 (q, 1H, J = 6.8 Hz), 6.7-7.4 (m, 5H), and 10.20 (s, 1H).

Anal. Calcd for $C_{11}H_{10}O_3Cl_2$: C, 50.60; H, 3.86. Found: C, 50.87; H, 3.74.

(Z)-1-METHOXY-2,2-DICHLORO-3-METHYLCYCLOPROPANECARBOXYLIC ACID: 82% yield; bp 114.0-118.0° (2.1 mm); mp 75.0-76.0° (from petroleum ether); ir (KBr) 3700-2200 (broad s), 1708 (vs), 1455 (m), 1425 (s), 1292 (vs), 1258 (s), 1206 (m), 1173 (m), 1040 (s), 877 (s), 840 (s), 743 cm^{-1} (m); ^1H NMR (CCl_4) δ 1.29 (d, 3H, J = 6.6 Hz), 2.43 (q, 1H, J = 6.6 Hz), 3.76 (s, 3H), and 12.24 (s, 1H).

Anal. Calcd for $C_6H_8O_3Cl_2$: C, 36.21; H, 4.05; Cl, 35.63. Found: C, 36.30; H, 4.11; Cl, 35.47.

(Z)-1,2,2-TRICHLORO-3-METHYLCYCLOPROPANECARBOXYLIC ACID: 84% yield; bp 110.0-113.0° (4.6 mm); mp 72.0-74.0° (from petroleum ether); ir (KBr) 3600-2100 (broad s), 1700 (vs), 1418 (m), 1280 (s), 1107 (m), 920 (m), 867 (m), 815 cm^{-1} (m); ^1H NMR (chloroform-d) δ 1.32 (d, 3H, J = 6.6 Hz), 2.71 (q, 1H, J = 6.6 Hz), and 10.81 (s, 1H).

Anal. Calcd for $C_5H_5O_2Cl_3$: C, 29.51; H, 2.48; Cl, 52.28. Found: C, 29.70; H, 2.51; 52.13.

PREPARATION OF CYCLOPROPYL BROMIDES (I, II, III, AND IV). METHOD A FOR I, III, AND IV. To a suspension of the silver salt (36.4 mmol) of the acid in 100 ml of carbon tetrachloride was rapidly added a solution of bromine (36.4 mmol) in 20 ml of carbon tetrachloride at 40-77°. After the addition was over, the reaction mixture was stirred at the same temperature for 2-4 hr. The solid was removed by filtration and was washed with a small amount of carbon tetrachloride. The filtrates were concentrated by vacuum evaporation to give the corresponding crude bromide in 60-80% yield.

METHOD B FOR II. The acid (21.8 mmol) was gradually add-

ed to a stirred suspension of lead tetraacetate (21.8 mmol) in 50 ml of anhydrous benzene. Stirring was continued at room temperature for an hour. To this solution was added anhydrous sodium bromide (21.8 mmol) in one portion at 60° under nitrogen atmosphere. After being kept at 70° for 3 hr, the reaction mixture was diluted with n-hexane. The resulting solution was washed with 10% perchloric acid and 10% aqueous sodium bicarbonate, dried over anhydrous sodium sulfate, and was concentrated under reduced pressure to give the crude bromide in 50-60% yield.

1-FLUORO-2,2-DICHLORO-3-METHYLCYCLOPROPYL BROMIDE (Ia AND Ib): 68% yield; bp 50.0-52.0° (19 mm); n_D^{18} 1.4754; ir (film) 2990 (w), 1455 (m), 1252 (m), 1146 (m), 1113 (m), 1096 (m), 996 (s), 862 (s), 828 cm^{-1} (m); ^1H NMR (CCl_4) δ 1.35 (d, 3H, J = 6.6 Hz) and 2.03 (dq, 1H, J = 6.6 and 7.2 Hz) for Ia, 1.33 (dd, 3H, J = 6.6 and 1.6 Hz) and 2.06 (dq, 1H, J = 6.6 and 19.8 Hz) for Ib; mass spectrum m/e (rel. abundance) no parent peak to 220, 205 (6), 192 (6), 185 (10), 141 (100), 121 (17), 105 (72), 85 (52).

1-PHENOXY-2,2-DICHLORO-3-METHYLCYCLOPROPYL BROMIDE (IIa AND IIb): 54% yield; bp 111.0-115.0° (4.5 mm); n_D^{21} 1.5680; ir (film) 2940 (m), 1592 (s), 1490 (s), 1448 (m), 1261 (s), 1239 (s), 1200 (s), 1169 (s), 1150 (s), 1142 (s), 1006 (s), 996 (s), 907 (s), 856 (s), 835 (s), 751 (s), 695 (s), 689 cm^{-1} (s); ^1H NMR (CCl_4) δ 1.40 (d, 3H, J = 6.6 Hz), 2.27 (q, 1H, J = 6.6 Hz), and 6.7-7.6 (m, 5H) for IIa, 1.45 (d, 3H, J = 6.6 Hz), 2.27 (q, 1H, J =6.6 Hz), and 6.7-7.6 (m, 5H) for IIb; mass spectrum m/e (rel. abundance) no parent peak to

300, 298 (2), 296 (5), 294 (3), 263 (10), 261 (37), 259 (29), 219 (2), 217 (10), 215 (15), 94 (27), 77 (100).

1-METHOXY-2,2-DICHLORO-3-METHYLCYCLOPROPYL BROMIDE (IIIa AND IIIb): 76% yield; bp 78.0-79.0° (15 mm); n_D^{20} 1.4869; ir (film) 2960 (m), 1450 (m), 1260 (m), 1240 (m), 1195 (m), 1135 (m), 1090 (m), 1043 (s), 945 (m), 880 (m), 780 (vs), 765 (s), 673 cm^{-1} (w); ^1H NMR (CCl_4) δ 1.30 (d, 3H, $\underline{J}$ = 6.6 Hz), 2.12 (q, 1H, $\underline{J}$ = 6.6 Hz), and 3.54 (s, 3H) for IIIa, 1.25 (d, 3H, $\underline{J}$ = 6.6 Hz), 1.84 (q, 1H, $\underline{J}$ = 6.6 Hz), and 3.54 (s, 3H) for IIIb; mass spectrum m/e (rel. abundance) 232 (P, 1), 221 (3), 219 (10), 217 (5), 201 (28), 199 (100), 197 (79), 157 (7), 155 (35), 153 (51), 109 (26), 107 (23), 105 (20), 103 (48).

1,2,2-TRICHLORO-3-METHYLCYCLOPROPYL BROMIDE (IVa AND IVb): 85% yield; bp 85.0-88.0° (24 mm); n_D^{27} 1.5239; ir (film) 2950 (w), 1446 (m), 1381 (w), 1104 (m), 902 (m), 852 (m), 829 (m), 803 cm^{-1} (m); ^1H NMR (CCl_4) δ 1.37 (d, 3H, $\underline{J}$ = 6.6 Hz) and 2.18 (q, 1H, $\underline{J}$ = 6.6 Hz) for IVa, 1.34 (d, 3H, $\underline{J}$ = 6.2 Hz) and 2.66 (q, 1H, $\underline{J}$ = 6.2 Hz) for IVb; mass spectrum m/e (rel. abundance) no parent peak to 236, 227 (2), 225 (8), 223 (12), 221 (6), 207 (4), 205 (26), 203 (58), 201 (36), 163 (6), 161 (50), 159 (95), 157 (100), 125 (10), 123 (55), 121 (88).

REDUCTION OF CYCLOPROPYL BROMIDES (I, II, III, AND IV) WITH TRI-$\underline{n}$-BUTYLTIN HYDRIDE. METHOD A. To a solution of the bromide (II or IV) (0.2-0.5 mmol) in 50 µl of $\underline{n}$-hexane was added dropwise 1.5 or 1.66 equiv of tri-$\underline{n}$-butyltin hydride with shaking under nitrogen atmosphere at a constant temperature. After the addition was over, the reaction mixture was kept at the same temperature with occasional shaking for 3

hr. The isomer composition of the product was measured by GLC and/or ^{1}H NMR spectroscopy prior to any further treatments.

METHOD B. Bromide (I or III) (0.2-0.5 mmol) was dropwise added to 1.5 or 4.5 equiv of tri-n-butyltin hydride with shaking under nitrogen atmosphere. After the reaction was over, it was followed by a similar treatment as above.

In all runs, GLC analyses showed that the reaction proceeded quantitatively. The isomer ratios of the products are accurate within ±2% and are summarized in Table II.

1-FLUORO-2,2-DICHLORO-3-METHYLCYCLOPROPANE (Vc AND Vd): bp 33.0-35.0° (42 mm); n_D^{25} 1.4356; ir (film) 2970 (m), 1452 (m), 1394 (m), 1260 (m), 1228 (m), 1143 (m), 1064 (m), 986 (s), 845 (s), 810 cm^{-1} (m); ^{1}H NMR (CCl_4) δ 1.26 (d, 3H, J = 6.6 Hz), 1.48-2.17 (m, 1H), and 4.16 (dd, 1H, J = 7.0 and 64.0 Hz) for Vc, 1.30 (d, 3H, J = 6.6 Hz), 1.48-2.17 (m, 1H), and 4.23 (dd, 1H, J =4.4 and 62.6 Hz) for Vd; mass spectrum m/e (rel. abundance) 146 (P+4, 1), 144 (P+2, 8), 142 (P, 12), 131 (5), 129 (33), 127 (44), 109 (36), 107 (100).

1-PHENOXY-2,2-DICHLORO-3-METHYLCYCLOPROPANE (VIc AND VId): bp 66.0-70.0° (0.5 mm); n_D^{19} 1.5368; ir (film) 2970 (m), 1600 (s), 1590 (s), 1494 (s), 1454 (m), 1230 (s), 1214 (s), 1170 (m), 1065 (m), 898 (m), 820 (m), 752 (s), 690 cm^{-1} (s); ^{1}H NMR (CCl_4) δ 1.28 (d, 3H, J = 4.6 Hz), 1.6-2.1 (m, 1H), 3.83 (d, 1H, J = 8.0 Hz), and 6.7-7.5 (m, 5H) for VIc, 1.40 (d, 3H, J = 5.4 Hz), 1.6-2.1 (m, 1H), 3.47 (d, 1H, J = 5.0 Hz), and 6.7-7.5 (m, 5H) for VId; mass spectrum m/e (rel. abundance) 220 (0.6), 218 (3), 216 (P, 5), 183 (7), 181 (20),

127 (4), 125 (22), 123 (33), 94 (100), 87 (21), 77 (25).

1-METHOXY-2,2-DICHLORO-3-METHYLCYCLOPROPANE (VIIc AND VIId): bp 55.0-56.0° (27 mm); n_D^{25} 1.4502; ir (film) 2950 (s), 1457 (s), 1387 (s), 1245 (s), 1130 (vs), 1110 (vs), 1052 (s), 1034 (vs), 953 (s), 868 (s), 846 (vs), 790 cm^{-1} (m); ^1H NMR (CCl_4) δ 1.13 (d, 3H, $\underline{J}$ = 6.4 Hz), 1.64 (dq, 1H, $\underline{J}$ = 6.4 and 8.4 Hz), 3.31 (d, 1H, $\underline{J}$ = 8.4 Hz), and 3.48 (s, 3H) for VIIc, 1.21 (d, 3H, $\underline{J}$ = 6.4 Hz), 1.61 (dq, 1H, $\underline{J}$ = 6.4 and 4.4 Hz), 2.94 (d, 1H, $\underline{J}$ = 4.4 Hz), and 3.47 (s, 3H) for VIId; mass spectrum m/e (rel. abundance) no parent peak to 154, 143 (2), 141 (12), 139 (18), 121 (33), 119 (100).

1,2,2-TRICHLORO-3-METHYLCYCLOPROPANE (VIIIc AND VIIId): bp 65.0-67.0° (52 mm); n_D^{28} 1.4760; ir (film) 2950 (m), 1448 (m), 1274 (m), 1133 (m), 1055 (m), 1026 (m), 907 (s), 834 (s), 806 (s), 725 cm^{-1} (m); ^1H NMR (CCl_4) δ 1.27 (d, 3H, $\underline{J}$ = 6.6 Hz), 1.5-2.2 (m, 1H), and 3.60 (d, 1H, $\underline{J}$ = 9.8 Hz) for VIIIc, 1.38 (d, 3H, $\underline{J}$ = 6.6 Hz), 1.5-2.2 (m, 1H), and 3.05 (d, 1H, $\underline{J}$ = 6.0 Hz) for VIIId; mass spectrum m/e (rel. abundance) 162 (1), 160 (2), 158 (P, 2), 127 (11), 125 (63), 123 (100), 89 (22), 87 (57).

REDUCTION OF METHYL ($\underline{Z}$)-α-PHENOXY- AND ($\underline{Z}$)-α-CHLORO-CROTONATE WITH LITHIUM ALUMINUM HYDRIDE. To a suspension of lithium aluminum hydride (0.03 mol) in 40 ml of anhydrous ether was added a solution of the ester (0.05 mol) in 10 ml of anhydrous ether at such a rate that gentle reflux could continued. After the addition was complete, the reaction mixture was refluxed for an hour, cooled to 0°, and was carefully treated with 5 ml of water. The resulting mixture was

poured into cold 10% sulfuric acid, followed by extraction with ether. The ethereal extracts were dried, concentrated, and distilled under reduced pressure to afford the corresponding crotyl alcohol.

(Z)-β-PHENOXYCROTYL ALCOHOL: 45% yield; bp 106.0-110.0° (3.5 mm); n_D^{24} 1.5340; ir (film) 3650-3100 (broad s), 2920 (m), 1688 (m), 1594 (s), 1486 (s), 1449 (m), 1286 (m), 1218 (s), 1164 (s), 1069 (s), 1024 (s), 1005 (s), 750 (s), 693 cm^{-1} (s); ^1H NMR (CCl_4) δ 1.54 (d, 3H, J = 7.2 Hz), 3.7-4.1 (m, 2H), 4.25 (broad s, 1H), 5.31 (q, 1H, J = 7.2 Hz), and 6.7-7.4 (m, 5H).

(Z)-β-CHLOROCROTYL ALCOHOL: 36% yield; bp 72.0-75.0° (23 mm); n_D^{18} 1.4680; ir (film) 3600-3000 (broad s), 2920 (m), 1665 (m), 1444 (m), 1296 (m), 1216 (s), 1145 (s), 1086 (s), 1025 (s), 1011 (s), 813 (m), 698 cm^{-1} (s); ^1H NMR (CCl_4) δ 1.77 (broad d, 3H, J = 6.6 Hz), 3.07 (broad t, 1H, J = 6.0 Hz), 4.07 (broad d, 2H, J = 6.0 Hz), and 5.79 (broad q, 1H, J = 6.6 Hz).

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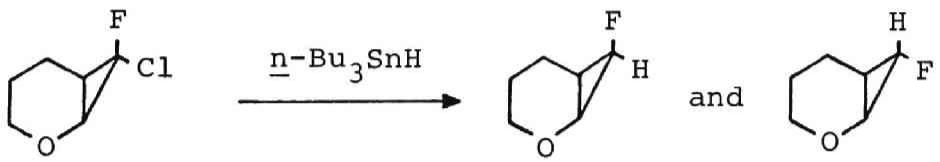
PART II

EFFECT OF β SUBSTITUENTS ON THE CONFIGURATIONAL STABILITY OF CYCLOPROPYL RADICALS

Chapter 1

INTRODUCTION

Much evidence has been accumulated for the configurational stability, or the energy barrier for inversion, of vinyl and cyclopropyl radicals, and the dependence of the configurational stability upon the nature of α substituents has been well recognized.[1] No attention, however, has ever been focussed on the possible effect of β substituents. The only one exception is the reduction of 7-halo-7-fluoro-2-oxanorcaranes with tri-n-butyltin hydride, which was carried out by Ando and co-workers.[2]



at 80°	84	16
130°	65	35
165°	5	95

They observed that the reduction proceeded with fairly high stereospecificity even below 130°, but at 165° with a large extent of inversion of configuration.

From the theoretical point of view, on the other hand, Dewar and Bingham[3,4] have very recently suggested the existence of a new, unsuspected β-substituent effect of obvious importance in radical chemistry.

This part is concerned with the effect of β substituents on the configurational stability of α-fluorocyclopropyl radicals. The stereochemistry of the reduction of 1-substituted 7-chloro-7-fluoronorcaranes with tri-n-butyltin hydride is discussed in detail.

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Chapter 2

REDUCTION OF 1-SUBSTITUTED 7-FLUORO-7-HALONORCARANES WITH TRI-n-BUTYLTIN HYDRIDE[1]

The stereospecificity of the reduction of 1-fluoro- (I), 1-methoxy- (II), 1-methyl- (III), and 1-unsubstituted-7-chloro-7-fluoronorcarane (IV) with neat tri-n-butyltin hydride has been measured and found to decrease in the order: III > IV > II > I. This suggests that the 1-methyl and the 1-fluoro or methoxy substituents, which are situated in the position β to the radical center, have the effect of increasing and decreasing, respectively, the configurational stability of the 7-fluoro-7-norcaryl radical.

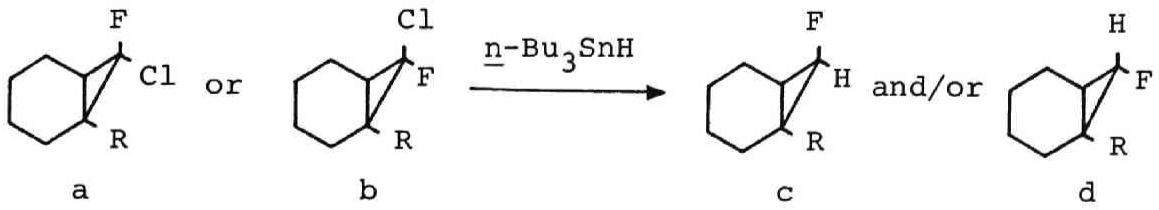
Recently, much work has been done on the configurational stability, or the energy barrier for inversion, of vinyl[2] and cyclopropyl[3] radicals, depending on the nature of α substituents. However, no studies have ever been made on the effect of β substituents, except the one made by Dewar and Bingham[4] from the theoretical point of view.

In this chapter is described the stereochemistry of the reduction of β-substituted α-fluorocyclopropyl halides with tri-n-butyltin hydride, which is believed to take place via α-fluorocyclopropyl radicals, one of the most stable radicals known. It offers the first experimental evidence for the existence of a new β-substituent effect on the configurational stability of the α-fluorocyclopropyl radicals.

RESULTS

1-Fluoro- (I), 1-methoxy- (II), 1-methyl- (III), and 1-unsubstituted-7-chloro-7-fluoronorcarane (IV) (Scheme) were prepared as an isomeric mixture (a and b) by the addition of chlorofluorocarbene, generated from the reaction of methyl dichlorofluoroacetate with sodium hydride and methanol at 30°,[5] to the corresponding cyclohexene. The stereochemical assignment to the isomers was made from their ^{19}F NMR spectra[6,7] (Table I). Preparative GLC[8] was used to separate the isomers, a and b, which were more than 99% pure. Each isomer was separately reduced under nitrogen atmosphere with neat tri-n-butyltin hydride by adding the latter (1.2 equiv) to the chloride in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) or di-tert-butyl peroxide (DTBP) at a constant temperature. The yields of reduction products (c and d) were measured from their peak areas in GLC, calibrated against authentic sample solutions of known concentrations. Where only isomer composition was desired, no inter-

SCHEME



a b c d

I, R = F

II, R = OMe

III, R = Me

IV, R = H

V, R = F

VI, R = OMe

VII, R = Me

VIII, R = H

nal reference was added.

The configurations of the isomers, c and d, were determined from their ^{1}H NMR spectra based upon the magnitude of vicinal couplings between ring hydrogens[9] (Table I).

The yields and the isomeric compositions of the products are summarized in Table II, together with the reaction conditions.

DISCUSSION

As shown in Table II, the reduction of 1-methyl-7-chloro-7-fluoronorcarane (III) proceeded with complete retention of configuration, whereas that of 1-fluoro- (I) or 1-methoxy-7-

TABLE I

NMR Parameters for Starting Halides and Reduction Products

Compd	Proton chemical shifts δ, ppm (J, Hz)	Fluorine chemical shifts δ_F, ppm (J, Hz)
Ia	0.8-2.5 (m, 9H)	88.5 (m), 77.5 (broad s, J = 8.8*)
Ib	0.9-2.5 (m, 9H)	97.1 (m), 63.5 (d, J = 28.8)
IIa	1.1-2.2 (m, 9H), 3.32 (s, 3H)	72.1 (broad s, J = 11.9*)
IIb	1.0-2.3 (m, 9H), 3.32 (s, 3H)	63.9 (d, J = 24.7)
IIIa	0.8-2.4 (m, 9H), 1.25 (d, 3H, J = 1.8)	70.0 (broad s, J = 9.8*)
IIIb	0.8-2.4 (m, 9H), 1.25 (d, 3H, J = 1.8)	55.5 (d, J = 19.4)
IVa	1.1-2.2 (m, 10H)	82.3 (broad s, J =5.2*)
IVb	1.1-2.2 (m, 10H)	47.8 (d, J = 18.9)
Vc	0.5-2.6 (m, 9H), 4.62 (ddd, 1H, J = 8.0, 13.0, 65.4)	90.3 (m), 155.3 (dd, J = 9.2, 65.4)
Vd	0.5-2.6 (m, 9H),	108.8 (m), 144.6 (dd, J = 28.4, 62.6)

(Continued)

	3.99 (broad d, 1H, $\underline{J}$ = 62.6)	
VIc	0.7-2.4 (m, 9H), 3.14 (s, 3H),	
	4.36 (dd, 1H, $\underline{J}$ = 8.0, 65.0)	149.4 (broad d, $\underline{J}$ = 9.7, 65.0)
VId	0.8-2.3 (m, 9H), 3.29 (s, 3H),	
	4.04 (dd, 1H, $\underline{J}$ = 3.0, 63.0)	144.3 (dd, $\underline{J}$ = 28.5, 63.0)
VIIc	0.5-2.3 (m, 9H), 0.97 (d, 3H, $\underline{J}$ = 2.4),	
	4.01 (dd, 1H, $\underline{J}$ = 7.6, 67.6)	147.8 (broad d, $\underline{J}$ = 11.6, 67.6)
VIId	0.6-2.2 (m, 9H), 1.16 (d, 3H, $\underline{J}$ = 1.8),	
	4.11 (dd, 1H, $\underline{J}$ = 2.0, 65.2)	138.7 (dd, $\underline{J}$ = 22.7, 65.2)
VIIIc	0.5-2.3 (m, 10H),	156.0 (broad d, $\underline{J}$ = 9.0, 68.0)
	4.39 (dt, 1H, $\underline{J}$ = 6.2, 68.0)	
VIIId	0.6-2.1 (m, 10H),	126.0 (dt, $\underline{J}$ = 18.0, 64.0)
	4.13 (dt, 1H, $\underline{J}$ = 1.8, 64.0)	

* Coupling constants are determined from half-height width of their resonance peaks.

TABLE II

Reduction of Halides (I, II, III, and IV)

with Tri-n-butyltin Hydride

Compd	Temp °C	Time hr	Yield %	Isomer ratio retn : invn
Ia	80	6	78	89 : 11
	140	3	84	77 : 23
Ib	80	6	80	79 : 21
	140	3	73	25 : 75
IIa	80	4	74	94 : 6
	140	1.5	75	79 : 21
IIb	80	4		88 : 12
	140	1.5		32 : 68
IIIa	80	10	70	100 : 0
	140	4	82	100 : 0
IIIb	80	10		100 : 0
	140	4		100 : 0
IVa	80	8	66	100 : 0
	140	4	74	96 : 4
IVb	80	8	68	98 : 2
	140	4	81	89 : 11

chloro-7-fluoronorcarane (II) occurred in a partially stereospecific manner to give a mixture of two geometrical isomers. The complete stereospecificity observed with III means that the inversion of configuration of the 1-methyl-7-fluoro-7-norcaryl radical intermediate occurs much more slowly than its hydrogen abstraction, and can be attributed to its extremely high configurational stability. On the other hand, it is suggested that the configurational stability of the 1-fluoro- or the 1-methoxy-7-fluoro-7-norcaryl radical is not so high as that of the 1-methyl-7-fluoro-7-norcaryl radical, and that its inversion of configuration takes place at a rate comparable to its hydrogen abstraction.

Table II also shows that the ratio of retention to inversion decreases as the reaction temperature increases. In the reaction of I at 140°, particularly, the isomer distributions in the products were essentially the same regardless of the starting chloride. This indicates that under these reaction conditions the inversion of configuration of the 1-fluoro-7-fluoro-7-norcaryl radical occurs much more rapidly than the hydrogen abstraction from the tin hydride.

From the stereochemical results described herein, it follows that in comparison with the 1-unsubstituted 7-fluoro-7-norcaryl radical, the 1-methyl and the 1-fluoro or methoxy substituents, which are situated at the position β to the radical center, have the effect of stabilizing and destabilizing, respectively, the pyramidal structure of the 7-fluoro-7-norcaryl radical. The origin of this β-substituent effect cited above is not clear, but its presence has been proposed

by Dewar and Bingham[4] from their semitheoretical studies.

Of more interest is that this novel-type effect of β substituents is in the order: fluoro > methoxy > hydrogen > methyl, which is opposite to the one encountered in the effect of α substituents of increasing the configurational stability of cyclopropyl radicals.[3,10]

EXPERIMENTAL SECTION

GENERAL. All boiling points are uncorrected. Infrared spectra were obtained on a Shimadzu IR-400 infrared spectrometer. A Varian Associates EM-360 spectrometer (60 MHz) was used to measure the proton NMR spectra for solutions in carbon tetrachloride with tetramethylsilane (Me_4Si) as an internal standard. Fluorine NMR spectra were recorded on a Hitachi H-60 (56.4 MHz) or R-20BK spectrometer (56.45 MHz) in carbon tetrachloride with trifluoroacetic acid (TFA) as an external reference. The proton and fluorine chemical shifts are expressed in parts per million downfield from Me_4Si and in parts per million upfield from TFA, respectively. Mass spectra were taken on a Hitachi RMS-4 mass spectrometer at 70 eV of an ionizing potential. Gas chromatography (GLC) was performed with Shimadzu GC-2C, GC-6A, and Jeolco JGC-20KT gas chromatographs by use of a 3 m x 3 mm glass column. Isomer distributions were calculated from the peak areas in gas chromatograms. The accuracy for the values of the isomer ratios listed in Table II is within ±2%.

MATERIALS. All chemicals were reagent grade and were used without further purification. Solvents were distilled or vacuum-distilled through a 25-cm Vigreux column and, if necessary, were purified in the conventional manner.

1-Methoxycyclohexene[11] and 1-methylcyclohexene[12] were prepared according to the literature procedure.

1-FLUOROCYCLOHEXENE. In a four-necked flask equipped with a mechanical stirrer, a thermometer, and a condenser with a drying tube were placed cyclohexene oxide (0.98 mol), potassium hydrogen fluoride (1.47 mol), and diethylene glycol (190g). This mixture was maintained at 170-175° with stirring for 1 hr, followed by vacuum distillation. The crude product was redistilled under reduced pressure to give 100g of trans-2-fluorocyclohexanol in 64% yield: bp 77.0-78.0° (22 mm) (lit. 68-69° at 14 mm[13]); n_D^{21} 1.4495; ir (film) 3400-3260 (broad s), 2970 (s), 1452 (s), 1385 (m), 1355 (m), 1233 (m), 1075 (vs), 1031 (vs), 925 (s), 856 cm^{-1} (s); ^1H NMR δ 0.6-2.4 (complex m, 8H), 3.33 (s, 1H, OH), and 3.2-4.0 (m, 2H). To a suspension of phosphorous tribromide (1.0 mol) and dried sodium bromide (0.8 mol) was added trans-2-fluorocyclohexanol (1.0 mol) with stirring at 150°. After being kept at the same temperature for 3 hr, the reaction mixture was poured onto ice water and was worked up as usual. Distillation of crude products gave cis-1-bromo-2-fluorocyclohexane as a pale yellow liquid in 56% yield: bp 68.0-70.0° (14 mm) (lit. 78° at 16 mm[13]); $n_D^{19.5}$ 1.4869 (lit. n_D^{20} 1.4891[13]); ir (film) 2950 (vs), 2875 (m), 1452 (m), 1375 (m), 1260 (m), 1210 (m), 1183 (m), 1146 (m), 1105 (m), 1055 (m), 962 (s), 855 (m),

810 (m), 705 cm^{-1} (m); ^1H NMR δ 1.0-2.6 (complex m, 8H), 3.8-4.5 and 4.9-5.1 (m, 2H). To a mixture of sodium methoxide (0.55 mol) in anhydrous dimethyl sulfoxide (200 ml) was added dropwise cis-1-bromo-2-fluorocyclohexane (0.50 mol) at room temperature over a period of 1.5 hr. The reaction mixture was stirred for several hours, followed by heating at 70° for 1 hr, and was quenched with water. The resulting solution was extracted four times with n-pentane. The combined organic extracts were washed twice with water, dried over anhydrous calcium chloride, and were distilled on a 25-cm Henninger-type column to give 1-fluorocyclohexene as a colorless liquid in 62% yield: bp 95.0-96.0° (lit. 96°[13]); $n_D^{17.5}$ 1.4299 (lit. n_D^{20} 1.4269[13], n_D^{25} 1.4251[14]); ir (film) 2938 (s), 2858 (m), 1702 (m), 1447 (m), 1374 (s), 1341 (m), 1134 (s), 974 (m), 922 (m), 858 (m), 800 (m), 781 cm^{-1} (m); ^1H NMR δ 1.66 (m, 4H), 2.11 (m, 4H), and 5.07 (broad d, 1H, J = 16.8 Hz); mass spectrum m/e (rel. abundance) 100 (P, 46), 85 (11), 72 (100), 59 (17).

PREPARATION OF 1-SUBSTITUTED 7-CHLORO-7-FLUORONORCARANES (I, II, III, AND IV). In a 300-ml four-necked flask fitted with a condenser, a mechanical stirrer, a thermometer, a dropping funnel, and an inlet tube for nitrogen was placed a mixture of sodium hydride (0.3 mol), 70 ml of anhydrous ether, methyl dichlorofluoroacetate (0.3 mol), and the corresponding cyclohexene (0.3 mol). To this mixture was added slowly absolute methanol (0.3 mol) under nitrogen at 25-35°. After the reaction mixture was allowed to stand overnight, a small amount of methanol, and subsequently 100 ml of water were

gradually added. The organic layer was separated, the aqueous layer was extracted three times with ether. The combined organic extracts were washed with aqueous sodium bicarbonate and with water, dried over anhydrous sodium sulfate, and were concentrated in vacuo. The resultant residual oil was distilled under reduced pressure to afford a colorless liquid.

Ia and Ib: 43% yield (Ia : Ib = 23 : 77); bp 52.5- 53.5° (15 mm); n_D^{18} 1.4418; ir (film) 2954 (vs), 2882 (m), 1452 (m), 1420 (m), 1340 (m), 1195 (m), 1162 (s), 1130 (vs), 1111 (s), 1065 (s), 1019 (s), 935 (s), 885 (s), 739 cm^{-1} (m); mass spectrum m/e (rel. abundance) 168 (P+2, 3), 166 (P, 8), 139 (13), 131 (59), 126 (35), 124 (100), 111 (25), 89 (26), 85 (24), 77 (10).

IIa and IIb: 59% yield (IIa : IIb = 43 : 57); bp 88.0-89.0° (21 mm); n_D^{18} 1.4637; ir (film) 2950 (s), 2860 (m), 1455 (m), 1250 (m), 1185 (m), 1135 (s), 1090 (s), 1080 (s), 1000 (s), 955 cm^{-1} (m); mass spectrum m/e (rel. abundance) 180 (P+2, 0.7), 178 (P, 2), 151 (10), 143 (100), 111 (34), 109 (13), 93 (21), 91 (12), 85 (13), 71 (14).

IIIa and IIIb: 48% yield (IIIa : IIIb = 25 : 75); bp 60.5-61.5° (20 mm); n_D^{20} 1.4581; ir (film) 2945 (vs), 2880 (m), 1452 (m), 1344 (m), 1221 (m), 1211 (m), 1188 (m), 1143 (m), 1099 (vs), 1064 (m), 1034 (m), 990 (m), 965 (m), 890 (m), 842 cm^{-1} (m); mass spectrum m/e (rel. abundance) 164 (P+2, 5), 162 (P, 14), 149 (11), 147 (26), 135 (4), 133 (16), 127 (100), 122 (11), 120 (32), 111 (22), 109 (12), 108 (12), 107 (33), 106 (33), 95 (17), 85 (55), 79 (24).

IVa and IVb: 51% yield (IVa : IVb = 34 : 66); bp 47.5-

49.0° (14 mm); n_D^{28} 1.4565; ir (film) 2935 (s), 2870 (m), 1450 (m), 1232 (m), 1090 (s), 1020 (m), 872 cm^{-1} (s).

REDUCTION OF 1-SUBSTITUTED 7-CHLORO-7-FLUORONORCARANES (I, II, III, AND IV) WITH TRI-n-BUTYLTIN HYDRIDE. A chloride (0.6 mmol) and a small amount of AIBN or DTBP were placed in a 5-ml flask, capped with a rubber septum fitted with a microthermometer, and the whole system was flushed with pure nitrogen before setting to a constant temperature and adding 1.2 equiv of tri-n-butyltin hydride by use of a syringe. After this mixture was allowed to stand with occasional swirling for several hours, carbon tetrachloride (0.5 ml) was added. The products were isolated by vacuum distillation. The isomer distributions in the products were determined by GLC before distillation and are given in Table II.

Vc and Vd: bp 64-71° (65 mm); $n_D^{18.5}$ 1.4255; ir (film) 2949 (s), 2874 (m), 1455 (m), 1435 (m), 1363 (m), 1345 (m), 1265 (m), 1195 (m), 1175 (m), 1124 (s), 1095 (m), 1062 (m), 977 (m), 935 (m), 912 (m), 895 (m), 845 (m), 694 cm^{-1} (m); mass spectrum m/e (rel. abundance) 132 (P, 10), 112 (7), 104 (22), 103 (29), 99 (40), 97 (13), 90 (100), 86 (12), 85 (16), 79 (15), 77 (12), 73 (12).

VIc and VId: bp 56.0-57.0° (17 mm); n_D^{18} 1.4449; ir (film) 2940 (s), 1458 (m), 1417 (m), 1343 (m), 1265 (m), 1208 (m), 1184 (m), 1160 (m), 1120 (s), 1088 (s), 1077 (s), 1023 (m), 700 cm^{-1} (w); mass spectrum m/e (rel. abundance) 144 (P, 18), 143 (13), 129 (13), 116 (50), 115 (100), 112 (25), 111 (48), 102 (13), 97 (23), 85 (33), 79 (18), 72 (33).

VIIc and VIId: bp 65.0-66.0° (55 mm); n_D^{20} 1.4383; ir

(film) 2937 (vs), 2862 (m), 1452 (m), 1421 (m), 1385 (w), 1184 (m), 1165 (m), 1133 (m), 1093 (s), 1063 (m), 960 (m), 828 cm^{-1} (w); mass spectrum m/e (rel. abundance) 128 (P, 60), 113 (52), 108 (6), 99 (58), 95 (100), 93 (29), 91 (14), 86 (87), 85 (78), 81 (42), 79 (22), 77 (19), 73 (20), 72 (41), 68 (37), 67 (67).

VIIIc and VIIId: bp 68.0-69.0° (107 mm); n_D^{28} 1.4376; ir (film) 2940 (s), 2865 (m), 1453 (m), 1435 (m), 1345 (w), 1222 (w), 1168 (m), 1077 (s), 1048 (m), 1015 (m), 850 cm^{-1} (m).

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PART III

CARBON-13 NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY FOR THE CYCLOPROPYL RING SYSTEMS

Chapter 1

INTRODUCTION

Applications of proton NMR spectroscopy to the elucidation of structural and stereochemical features of organic compounds have been well established[1] and have been routinely exploited, but for numerous systems the information available from proton NMR is either limited or somewhat difficult to interpret unequivocally. In principle, structural and stereochemical information for a wide variety of systems is provided by NMR parameters of several other nuclei. One of the most potent sources of such data is carbon-13 nucleus. The tremendous strides taken in advancement of carbon-13 NMR techniques and instrumentation over the past four or five years have made the carbon-13 spectroscopy a routine chemical tool offering powerful new approaches to the solution of a wide range of problems. Carbon-13 nuclear magnetic resonance (cmr) has now become almost an everyday tool in the hands of practicing chemists. Large amounts of data on an enormous variety of compounds are available,[2-7] and can be effectively used as a means of identification or location of substituents.

In contrast to protons, carbon-13 nuclei absorb over a

relatively wide range which is about 220 ppm for commonly-encountered, neutral organic compounds. The most highly shielded carbon in a diamagnetic environment yet reported is that of carbon tetraiodide,[8] δ_C -292, while charge-bearing carbons in alkyl carbocations absorb as low as δ_C 334.[9] Since carbon-13 spectra are routinely recorded with complete proton decoupling, they consist entirely of singlet signals (provided other magnetic nuclei are absent), and usually well-resolved signals are seen for each individual carbon in molecules of moderate complexity. For example, even the spectra of steroids generally have few, if any, overlapping signals. Consequently, carbon-13 spectra are potentially rich sources of information on shielding (chemical shift).

One striking feature of carbon shieldings is that a simple additivity rule applies with good precision, i. e., the difference in shielding can be accounted for as a sum of substituent effects, so long as closely related compounds are concerned.[2-4]

The effect of a variety of substituents derived for aliphatic hydrocarbon derivatives is listed in Table I,[2-4] from which it is apparent that appreciable effects are observed at α, β, and γ carbons, and even at carbons four and five bonds apart from the substituent. The trends illustrated in Table I have not yet been quantitatively understood. Nevertheless qualitative, empirical interpretations of these substituent effects have been extremely useful in the study of organic compounds by carbon-13 NMR spectroscopy.

Substituent parameters have been so far derived for a

TABLE I

Substituent Effects[a] in Aliphatic Systems

Substituent	α	β	γ	δ	ε
Me	9.1	9.4	-2.5	0.3	0.1
Cl	31.2	10.5	-4.6	0.1	0.5
Br	20.0	10.6	-3.1	0.1	0.5
1°-I	-10.0[b]	11.3	-1.0	0.2	1.0
1°-OH	48.3	10.2	-5.8	0.3	0.1
2°-OH	40.8	7.7	-3.7	0.3	0.3
1°-NH_2	28.9	11.4	-4.6	0.7	-
COOH	20.9	2.5	-2.2	1.0	-

[a] Substituent shifts are expressed in parts per million (ppm). Negative and positive values denote upfield and downfield shifts, respectively. [b] Marker, et al.,[11] found the α effects in isopropyl iodide and tert-butyl iodide to be +1.4 and +13.7 ppm, respectively.

number of functional groups on aliphatic and aromatic frameworks,[2-4] but little work has been done with cyclopropane derivatives. Only for simple cyclopropanes the effect of substituents has been studied extensively.[10]

In this part, carbon-13 NMR spectra of a series of endo- and exo-7-substituted and 7,7-disubstituted norcaranes are described. The effect of substituents on carbon shieldings is discussed in detail, as well as carbon-fluorine and carbon-hydrogen couplings.

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Chapter 2

CARBON-13 NMR SPECTROSCOPY FOR 7-SUBSTITUTED AND 7,7-DISUBSTITUTED NORCARANES

Fourier transform carbon-13 nuclear magnetic resonance spectra were measured for a number of endo- and exo-7-substituted and 7,7-disubstituted norcaranes. The substituent shift parameters were calculated from a series of 7-monosubstituted norcaranes and were used for predicting the shifts of stereoisomers of some 7,7-disubstituted norcaranes. The agreement between the observed and the calculated shifts was satisfactory, proving the validity of this general approach. Interpretation of the observed substituent shifts in terms of steric and electronic effects has shown: (i) The α and β substituent effects as well as the γ gauche and anti effects are dependent on the relative orientation of the substituent on the α carbon, and (ii) A long-range γ anti effect produced on the γ carbon nuclei by the exo 7-substituent can be explained more reasonably by the back-lobe interaction mechanism than by the hyperconjugative interaction mechanism. Several ^{13}C-^{19}F and ^{13}C-^{1}H coupling constants are also reported and interpreted in terms of the s character of the C-F and C-H bonds,

respectively.

Carbon-13 nuclear magnetic resonance (cmr) spectroscopy has now become one of the most useful research techniques available for stereochemical assignment and structural elucidation of organic compounds. These applications are, for the most part, based upon empirical correlations between carbon-13 shieldings and molecular geometry.[1] The carbon-13 magnetic resonance spectra of a number of molecules containing hetero substituents have been recorded and interpreted in terms of inductive, steric, and bond delocalization effect.[2-8] In the literature, however, there is no systematic investigation on the conformational and substituent factors, which affect carbon-13 shieldings, in cyclopropyl ring systems possessing hetero substituent(s).

The carbon chemical shifts for a series of norcarane derivatives have now been determined. These compounds were chosen because the norcaryl skeleton provides a relatively rigid and stereochemically defined framework suitable for the investigation of substituent effects. The aim of the present study is to determine steric and substituent shift factors and to investigate their variations due to the orientational changes of a substituent on the norcaryl skeleton. This will make it possible to test quantitatively the validity of the theories and speculations which have been advanced to explain carbon-13 shieldings on an electronic ground.

EXPERIMENTAL SECTION[9]

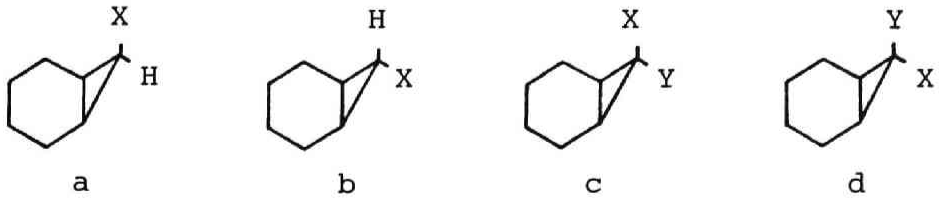
MATERIALS. All 7,7-disubstituted norcaranes except 7-chloro(and -bromo)-7-methoxycarbonylnorcaranes were obtained by the addition of the corresponding halocarbene to cyclohexene.[10] 7-Chloro(and -bromo)-7-methoxycarbonylnorcaranes were prepared by the carbonation of 7-chloro(or -bromo)-7-norcaryllithium with solid carbon dioxide followed by esterification with the conventional procedure.[11] 7-Monosubstituted norcaranes were obtained by the reduction of the corresponding 7-norcaryl halides with tri-n-butyltin hydride.[12] Only 7-methoxynorcarane was synthesized according to the previously reported method.[13] Separation of isomers of these compounds was achieved by use either of preparative gas chromatography (GLC) or of thermal decomposition of an isomeric mixture in hot quinoline.[14] Stereochemistry of the isomers was determined on the basis of their proton and fluorine magnetic resonance spectra and of the difference in rate of the thermal decomposition in hot quinoline.[14]

SPECTRA. ^{13}C NMR spectra were recorded on a Varian Associates CFT-20 computer-controlled spectrometer operating at 20 MHz. The Fourier transform (FT) technique was applied.[15] Samples for measurement were prepared as 0.2-0.4 M solutions in chloroform-d with tetramethylsilane (Me_4Si) as an internal standard. All chemical shifts were determined from proton noise decoupled (PND) spectra and are expressed in parts per million downfield from Me_4Si. The precision of the computer-measured chemical shifts is within ±0.1 ppm (4K data points

in the time-domain spectra for a 200-ppm spectral width) and narrow peaks as close as 0.1 ppm can be resolved. Single frequency off-center decoupled (sfocd) (off-resonance) spectra were used to assign the resonance of carbons in questionable cases. In a few instances, spectra were taken on an isomeric mixture because of the difficulties in separation of the isomers. The resonance lines due to each component in the mixture could be readily identified from their intensities because the components were present in unequal amounts in all cases. The chemical shifts determined for an isomer alone or as an isomeric mixture were practically identical.

RESULTS

In almost all proton noise decoupled (PND) spectra, four signals generally appeared except those due to the carbon(s) contained in the substituent because of the presence of an element of symmetry in the norcaryl system studied. The chemical shifts for the series of 7-substituted and 7,7-disubstituted norcaranes are given in Tables I and II, respectively, in parts per million downfield from internal Me_4Si. The assignment for four signals in the spectrum of norcarane (I) was made as follows: carbon (7) and carbons (1,6) were assigned from the off-resonance experiment because this technique splits the carbon signals according to the number of directly attached hydrogen. The assignment for carbons (2,5) and carbons (3,4) was unambiguously made on the basis of the cri-



a b c d

I, X = H

II, X = F

III, X = Cl

IV, X = Br

V, X = OMe

VI, X = COOMe

VII, X = Ph

VIII, X = Me

IX, X = F; Y = Cl

X, X = F; Y = Br

XI, X = Cl; Y = Br

XII, X = Cl; Y = Ph

XIII, X = Cl; Y = COOMe

XIV, X = Br; Y = COOMe

XV, X = Y = Cl

XVI, X = Y = Br

terion that substitution with a methyl or a methylene group causes a downfield shift at both the α and β carbons and an upfield shift at the γ carbons.[1] Further confirmation of this assignment was obtained by comparison with the relative chemical shifts of the α and β carbons in decalin.[16] In the case of fluorinated compounds, 7-fluoronorcarane (II), 7-chloro-7-fluoronorcarane (IX), and 7-bromo-7-fluoronorcarane (X), the observation of C-F coupling constants and the dependence of their magnitude on the number of intervening bonds made a straightforward assignment possible for all carbon nuclei (Table V). The α carbon, C-7, has the largest $\underline{J}$ value, followed by the β carbons, C-1,6, and the γ carbons, C-2,5. The

TABLE I

Carbon-13 Chemical Shifts in Endo and Exo 7-Substituted Norcaranes

Compd	X	C-7	C-1,6	C-2,5	C-3,4	Others
I	Nil	10.6	9.8	24.4	21.8	
			Endo derivatives			
IIa	F	74.7	11.1	17.7	22.4	
IIIa	Cl	40.0	12.5	18.6	21.8	
IVa	Br	33.4	12.3	20.1	21.6	
Va	OMe	60.4	11.6	18.3	22.6	58.0
VIa	COOMe	22.1	16.6	18.9	21.5	50.8, 172.1(C=O)
VIIa	Ph	22.4	12.9	20.4	21.9	138.6, 128.2(o), 131.3(m), 125.8(p)
VIIIa	Me	12.2	10.4	18.9	22.9	8.3

(Continued)

Exo derivatives

IIb	F	79.5	17.0	21.9	21.7	
IIIb	Cl	37.9	21.5	22.5	21.4	
IVb	Br	25.3	21.6	22.7	21.1	
Vb	OMe	66.4	17.7	22.7	22.0	57.4
VIb	COOMe	25.9	22.1	23.1	21.3	51.2, 174.7(C=O)
VIIb	Ph	28.9	22.5	23.8	21.6	144.5, 125.4(o), 128.2(m), 125.0(p)
VIIIb	Me	18.0	18.4	24.0	22.0	19.0

TABLE II

Carbon-13 Chemical Shifts in Some 7,7-Disubstituted Norcaranes

Compd	C-7	C-1,6	C-2,5	C-3,4	Others
IXc	95.7	22.8	17.5	21.1	
IXd	101.7	21.2	20.5	18.4	
Xc	85.2	23.7	17.4	21.1	
Xd	97.1	22.0	20.3	19.6	
XIc	51.8	26.7	19.1	20.5	
XId	58.2	26.9	20.1	20.6	
XIIc	55.2	21.4	19.3	21.2	145.1, 127.1(o), 128.3(m), 127.1(p)
XIId	48.5	24.7	20.7	20.6	138.0, 128.8(o), 130.9(m), 128.0(p)
XIIIc	56.9	24.6	18.8	21.0	52.9, 179.8(C=O)
XIVd	32.2	25.9	19.6	20.7	52.6, 172.7(C=O)
XV	67.5	26.2	19.0	20.4	
XVI	40.4	27.2	20.2	20.7	

δ carbons, C-3,4, have the smallest or zero $\underline{J}$ value. The assignment presented here clearly demonstrates the great utility of fluorine substitution for the identification of carbon-13 resonances. Sfocd experiments were not performed on these fluoro compounds since several carbon signals were split by fluorine nucleus, giving a complex sfocd spectrum. The assignment for carbon resonances in spectra of nonfluorinated compounds was made by comparison with those of 7-fluoronorcarane. The δ carbons (C-3,4) were readily assigned since they are distant from the 7-substituent(s) enough to be invariant in their chemical shift. For the differentiation of the α carbon (C-7) from the β carbons (C-1,6), their relative intensities could be a good aid in addition to the larger downfield shift on the α carbon caused by the 7-substituent(s). The assignment was further confirmed from the sfocd experiments.

Table V compiles the C-F coupling constants observed for several fluoro compounds. The $\underline{J}_{CF}$ values on 7-fluoronorcarane (II) were in good agreement with those found for the other two fluoronorcaranes with exception of the one-bond coupling constant $^{1}\underline{J}_{CF}$, which had a value of 221.6 Hz. An additional polar substituent caused a further increase in the algebraic sense in the $^{1}\underline{J}_{CF}$ value (assumed to be of negative sign[17]) and this increase was similar to the one observed in other studies on the series of fluoromethanes.[18,19] Inspection of the one-bond coupling constants $^{1}\underline{J}_{CF}$ on 7-chloro-7-fluoronorcarane (IX) and 7-bromo-7-fluoronorcarane (X) reveals that the magnitude is strongly dependent upon the relative orien-

tation of the fluorine atom on the norcaryl skeleton: the directly bonded carbon is more strongly coupled with the exo-fluorine nucleus than with the endo one. A similar trend was observed for the direct C-H coupling constants $\underline{J}_{CH}$ as shown in Table VI. The geminal and vicinal coupling constants, $^{2}\underline{J}_{CF}$ and $^{3}\underline{J}_{CF}$, were slightly different between the endo- and the exo-fluoro isomers. Carbons more than three bonds apart (the δ carbons) can be coupled with the fluorine nucleus when they are close together in space. Thus, a long-range coupling occurred on the endo-fluoro isomers with a value of 1.1-2.0 Hz whereas on the exo counterparts with a zero value. This variation in $^{4}\underline{J}_{CF}$ has an important bearing on the theory of coupling constants between heavy nuclei, because it shows that a through-space interaction contributes significantly to the overall effects.[20]

Table VI lists the direct C-H coupling constants determined from natural-abundance experiments of some 7-substituted norcaranes.

DISCUSSION

The data given in Tables I to IV demonstrate that a substituent can have a substantial influence on the chemical shifts for the α (C-7), β (C-1,6), and γ (C-2,5) carbons but has a very little effect on that for the δ (C-3,4) carbons. Though smaller and subtler changes at the δ carbons may be proved of significance in the future, the α, β, and γ effects

TABLE III

Substituent Chemical Shifts

in Endo and Exo 7-Substituted Norcaranes[a]

Compd	X	C-7(α)	C-1,6(β)	C-2,5(γ)	C-3,4(δ)
		Endo derivatives			
IIa	F	-64.1	-1.3	6.7	-0.6
IIIa	Cl	-29.4	-2.7	5.8	0.0
IVa	Br	-22.8	-2.5	4.3	0.2
Va	OMe	-49.8	-1.8	6.1	-0.8
VIa	COOMe	-11.5	-6.8	5.5	0.3
VIIa	Ph	-11.8	-3.1	4.0	-0.1
VIIIa	Me	-1.6	-0.6	5.5	-1.1
		Exo derivatives			
IIb	F	-68.9	-7.2	2.5	0.1
IIIb	Cl	-27.3	-11.7	1.9	0.4
IVb	Br	-14.7	-11.8	1.7	0.7
Vb	OMe	-55.8	-7.9	1.7	-0.2
VIb	COOMe	-15.3	-12.3	1.3	0.5
VIIb	Ph	-18.3	-12.7	0.6	0.2
VIIIb	Me	-7.4	-8.6	0.4	-0.2

[a] Substituent shifts are in parts per million relative to norcarane (I); a negative sign denotes a downfield shift on substitution.

alone will be discussed here.

THE α AND β EFFECTS. As is clear from the data in Table III, the order of the chemical shifts of the α carbon is in essential agreement with that of the electronegativity for substituents. This tendency has also been found in cyclohexane,[21] bicyclo[2.2.2]octane,[22] and adamantane derivatives.[23] The most probable explanation for this variation is that it comes from the immediate electronic distribution about the carbon (7) nucleus and the neighbor anisotropy effect exerted by the 7-substituent. The carbon signals due to the β carbons move to a more downfield region as the electronegativity of the substituents decreases; this is in harmony with the shifts reported for the β carbons in adamantane derivatives.[23] The neighbor anisotropy effect seems to be grossly diminished in the β shifts. The magnitudes in the α and β effects are somewhat smaller than those observed in acyclic systems.[1] This is possibly due to the lower sensitivity of the highly-strained cyclopropyl ring systems to these substituents. It is apparent, however, that these substituents exhibit effects similar to those found in acyclic and alicyclic systems.[1]

Especially significant is the fact that the orientation of the substituent on the norcaryl skeleton has a profound effect on the magnitudes of the α and β shifts as well as of the γ shifts. As is shown in Table IV, which lists the difference between chemical shifts for endo- and exo-7-substituted norcaranes, the shifts caused by the endo substituents are consistently smaller by 2-10 ppm than by the exo substituents except for chlorine and bromine. It is not possible

TABLE IV

Difference between Chemical Shifts

of Endo and Exo 7-Substituted Norcaranes[a]

Substituent	C-7(α)	C-1,6(β)	C-2,5(γ)	C-3,4(δ)
F	4.8	5.9	4.2	-0.7
Cl	-2.1	9.0	3.9	-0.4
Br	-8.1	9.3	2.6	-0.5
OMe	6.0	6.1	5.4	-0.6
COOMe	3.8	5.5	4.2	-0.2
Ph	6.5	9.6	3.4	-0.3
Me	5.8	8.0	5.1	-0.9

[a] A negative value indicates that the resonance of endo compound is downfield relative to that of the corresponding carbon in exo one.

to decide whether this difference comes from an electronic basis or is caused by slight difference in the molecular geometry, since the endo substituents may introduce additional steric interaction which could be partially relieved by some distortion of the norcaryl skeleton. However, the difference between the effects for endo and exo orientations of 7-substituents is much larger than that observed in 2-substituted

norbornanes.[8] Such a situation can be attributed to the steric elongation of the C_α-C_β bond due to an endo substituent. Elongation of this bond will, according to the theory of Litchman and Grant,[24] produce upfield shifts at the α and β carbons.

In the case of 7,7-disubstituted norcaranes, as given in Table II, an additional polar substituent has a major effect on the chemical shifts for the α, β, and γ carbons in this order but has little effect on the δ carbons. One of the most important features is the fact that the chemical shift for the α carbon is in good agreement with the one calculated from a set of the corresponding substituent parameter compiled in Table III and the chemical shift of carbon (7) in the parent compound. For example, the observed shift for the α carbon in exo-7-bromo-endo-7-fluoronorcarane (Xc) is 85.2 ppm and the calculated value is 89.4 ppm, which is the sum of 64.1 ppm for endo-7-fluorine substitution, 14.7 ppm for exo-7-bromine substitution, and 10.6 ppm for carbon (7) in norcarane. In all cases except 7-chloro-7-fluoronorcarane, the deviation of the calculated from the observed values falls within the difference between the chemical shifts for the α carbon in each set of stereoisomers. Thus, the chemical shift calculated from the data in Table III allows stereochemical assignment to these related compounds, which otherwise is often very troublesome.

THE γ EFFECTS. Grant and his co-workers[3,25] have presented a semitheoretical rationalization for the sterically induced upfield shifts caused by hydrogen-hydrogen gauche in-

teractions. According to their proposal, such sterically nonbonded interactions can exert a polarization of the C-H bond such that the electron density moves from the hydrogen to the carbon and thus the carbon nucleus of interest is shielded. The importance of these steric interactions on carbon shieldings has been verified in other studies.[6-8,26] The present work is no exception and in fact, as shown in Table III, the sterically induced γ shifts are most easily recognized for overall series of endo-7-substituted norcaranes. In these compounds, the upfield shift must come from interactions between the hydrogen at the γ carbon and the lone pair or π electrons on a substituent. The same type of argument has been made for the upfield shift observed in norbornane derivatives,[8] where the magnitude of this shift increases as the size of a polar substituent becomes large. The magnitude of the γ gauche effect given in Table III, however, does not correlate simply with the bulkiness of substituents nor with their electronic property; e. g., chlorine and methoxycarbonyl groups have the effect of the same order of magnitude, in spite of the substantial difference in electronegativity. These results suggest the dependence of the γ gauche effect on the nonbonded distance between the hydrogen attached to the γ carbon and an interacting substituent. This distance, which has been measured using a Dreiding stereomodel, is nicely correlated with the magnitude for the observed γ gauche effect.

On the other hand, the data compiled in the lower half of Table III clearly demonstrate that the signal of the γ carbon nucleus anti to a polar substituent generally appears at

a significantly higher field than that of the parent compound. The γ carbons (C-2,5) in exo-7-substituted norcaranes are invariably shielded by the exo substituents. It is evident that this effect cannot be explained in terms of sterically nonbonded interactions discussed above. The upfield shift of this type has also been observed in the studies on several other compounds.[8,27,28] Two mechanisms have been proposed to explain the γ anti effect. The first mechanism[8,27] involves back-lobe interactions of the bonding orbitals on the γ carbon with those on the α carbon used to bind a polar substituent, by analogy with the model used to explain long-range spin-spin coupling through a "W" arrangement of bonds.[29] The other is hyperconjugative interactions of free-electron pairs on a substituent with the C_α-C_β bond accompanied by a subsequent alternation of the electron density at the γ anti carbon. The latter mechanism was recently suggested by Eliel, et al.,[28] for the apparently unique role which the second-row heteroatoms (e. g., N, O, and F elements) do play but the third-row elements (e. g., Cl and S elements) do not in the γ anti effect. At a glance of the data in Table III, it can be noted that almost all substituents have a profound effect on the chemical shifts for the γ anti carbons. The magnitude of the upfield shift due to chlorine or bromine is nearly identical with that due to the methoxy group, and even other groups (i. e., methoxycarbonyl and phenyl groups) have non-negligible effects. The order of the γ anti effect in magnitude appears to correlate roughly with the electronic nature of the substituents and this correlation has also been found

in norbornane derivatives.[8] Consideration of such situations prefers the back-lobe interaction mechanism for explaining the γ anti effect, although there exist no tools available to unravel the physical basis for this. The contrast between these data and those obtained by Eliel and his co-workers,[28] which apparently lack the γ shielding due to anti-periplanar third-row heteroatoms, seems to be due to the slight difference in rigidity of molecular framework. The results obtained here would provide a further opportunity to examine the mechanistic interpretation of the γ anti effect.

^{13}C-^{19}F AND ^{13}C-^{1}H COUPLING CONSTANTS. Table V demonstrates that the one-bond coupling constants $^{1}J_{CF}$ are markedly affected by additional substitution and that the one-bond couplings $^{1}J_{CF}$ and the long-range couplings $^{4}J_{CF}$ are dependent on the relative orientation of the C-F bond on the norcaryl skeleton. Previously, it was suggested that the largest $^{1}J_{CF}$ value occurs for the most strongly deshielded fluorine nucleus and there is a tendency for $^{1}J_{CF}$ (assumed to be of negative sign[17]) to decrease, i. e., to become more positive, with increasing ^{19}F shielding.[18] This is not necessarily the case. Endo fluorinated compounds have larger $^{1}J_{CF}$ values than exo counterparts, whereas in their ^{19}F NMR spectra[30] the endo-fluorine nucleus is invariably more strongly shielded than the exo one. This trend is analogous to that found for the direct C-H couplings (Table VI) but the relative signs are opposite. It seems that the major factor contributing to $^{1}J_{CF}$ includes the s character of the carbon orbital in the C-F bond; the $^{1}J_{CF}$ value decreases in magnitude with increase of the s

TABLE V

^{13}C-^{19}F Coupling Constants in Fluoro Compounds[a]

Compd	$^{1}J_{CF}$	$^{2}J_{CF}$	$^{3}J_{CF}$	$^{4}J_{CF}$
IIa	221.6	10.6	4.8	1.1
IIb	221.6	10.6	3.4	0
IXc	289.8	11.0	2.8	2.0
IXd	282.4	11.3	2.7	0
Xc	305.6	10.2	3.1	1.7
Xd	295.6	10.5	2.6	0

[a] All coupling constants are in hertz.

character. In the case of vicinal couplings $^{3}J_{CF}$, the carbons at the position cis to fluorine have larger coupling constants than the ones trans to fluorine. An apparently similar trend can be noted with the vicinal H-H[31] or H-F[32] coupling in the cyclopropyl ring systems. Of more importance is that the long-range coupling of carbon nuclei separated by four bonds with fluorine occurs in endo fluorinated compounds. This is closely related with their proximity in space, which indicates the contribution of through-space interactions to this effect.

As shown in Table VI, the magnitudes of the direct C-H coupling constants are dependent upon the nature of 7-substi-

TABLE VI

^{13}C-^{1}H Coupling Constants on Carbon (7) in Some 7-Substituted Norcaranes[a] (RX[b])

Compd	X	$\underline{J}_{CH}$ Endo-X	$\underline{J}_{CH}$ Exo-X
I	H	154.6	
II	F	196.8	194.5
III	Cl	189.0	186.5
IV	Br	187.8	c
V	OMe	179.5	177.4

[a] See footnote a in Table V. [b] R stands for 7-norcaryl group. [c] No value could be obtained owing to overlapping with other signals.

tuents and are in good agreement with those reported for other monosubstituted cyclopropanes.[33] The magnitudes, furthermore, depend slightly on the relative orientation of the C-H bond with respect to the cyclopropyl ring, though the difference is relatively small. It is well known that the coupling constant $\underline{J}_{CH}$ correlates with the s character of carbon in the C-H bond of interest: the equation $\underline{J}_{CH}$ = a(%s) - b generally applies though the values of a and b vary with the author.[34] If the approximate relationship $\underline{J}_{CH}$ = (5.70)(%s) -18.4[35] is

used to estimate the s characters of the carbon atoms at the position 7 in these compounds, they fall in the range of 30.4-37.8%, which corresponds to the hybridization state of $sp^{2.3}$-$sp^{1.7}$. These values may be regarded as satisfactory.

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PART IV

CONCLUSION

1. By use of the brominative decarboxylation (Hunsdiecker reaction) of α-substituted cyclopropanecarboxylic acids, the thermal decomposition of their tert-butyl peroxy esters, and the reduction of α-substituted cyclopropyl halides with tri-n-butyltin hydride, six α-substituted cyclopropyl radicals, viz., α-fluoro-, α-phenoxy-, α-methoxy-, α-chloro-, α-phenyl-, and α-methylcyclopropyl radicals, were generated and their configurational stability (the energy barrier for inversion) was evaluated by determining the stereospecificity of these reactions.

The reactions which occur via cyclopropyl radicals having a relatively electronegative atom or group such as fluoro, phenoxy, methoxy, or chloro at the α position proceeded with extremely or fairly high stereospecificity, whereas those reactions which occur via α-phenyl- or α-methylcyclopropyl radical proceeded with little or no stereospecificity. The former finding indicates that the α-fluoro-, the α-phenoxy-, the α-methoxy-, and the α-chlorocyclopropyl radicals have a pyramidal structure and the inversion of their configurations

occurs at a rate slower than or comparable to that of their hydrogen or bromine abstraction from scavenger molecules. The latter finding demonstrates that the α-phenyl- and the α-methylcyclopropyl radicals are either pyramidal but invert their configurations so rapidly that they behave as if they were planar, or in fact are planar.

The stereospecificity observed in these reactions can be correlated with the configurational stability of these radical intermediates, and the degree of the stereospecificity decreased in the order, α-fluoro- > α-phenoxy- > α-methoxy- > α-chlorocyclopropyl derivatives. It means that the α-fluorocyclopropyl radical is configurationally most stable, followed by the α-phenoxy- and the α-methoxycyclopropyl radicals, and the α-chlorocyclopropyl radical is least stable. This order of the configurational stability is closely related to the electronegativity of the substituent located α to the radical center. The conclusion is that the electronegativity of the α substituent can be a measure for evaluating the configurational stability of the cyclopropyl radical.

2. The stereochemistry of the reduction of β-substituted α-fluorocyclopropyl halides with tri-n-butyltin hydride was examined. It has been found that the β-methyl substituent has the effect of stabilizing, whereas the β-methoxy and β-fluoro substituents have the effect of destabilizing, the pyramidal structure of the α-fluorocyclopropyl radical. This offers the first experimental evidence for the existence of a new β-substituent effect on the configurational stability of cyclopropyl radicals. Of most importance is that the stabilizing

effect of β substituents follows the order, fluoro < methoxy < (hydrogen) < methyl substituents, and that this order is opposite to the one observed for the stabilizing effect of α substituents.

3. Carbon-13 NMR spectra were measured on sixteen 7-substituted or 7,7-disubstituted norcaranes.

The data demonstrated that a substituent can have a substantial influence on the chemical shifts of the α (C-7), β (C-1,6), and γ (C-2,5) carbons but have very little effect on the δ (C-3,4) carbons. The magnitudes of the α and β effects are somewhat smaller than those reported for acyclic hydrocarbon derivatives. Probably this comes from the less sensitivity of the highly strained cyclopropyl ring systems to polar substituents, as well as from the secondary nature of the carbon carrying the substituent. The magnitudes of the α and β shifts also depend upon the orientation of the substituent on the norcaryl skeleton, and the shifts caused by endo substituents are consistently 2 to 10 ppm smaller than those caused by exo substituents. The substituent shift parameters derived from the spectra of a series of 7-substituted norcaranes have been used to predict the shifts of 7,7-disubstituted norcaranes. The agreement between the observed and the calculated values is satisfactory enough to support the general approach.

The sterically induced γ shift, or the γ gauche effect, was observed most distinctly in all the endo stereoisomers. The magnitudes of this effect are related with the nonbonded distance between the hydrogen attached to the γ carbons and

an interacting substituent. In the case of the exo stereoisomers, although the γ carbons are invariably shielded by exo substituents, the degree of the γ anti effect is lower than that of the γ gauche effect. Almost all the polar substituents have a nonnegligible effect of this type and the order of the magnitude appears to be related with the electronic nature of the substituents. This γ anti effect can be explained most satisfactory by the back-lobe interaction, one of the earlier proposed mechanisms.

These steric and electronic effects on the α, β, and γ shifts may be a good aid to the stereochemical assignment and the structural elucidation of norcarane and related compounds, which otherwise are often very troublesome.

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